Brain

A Journal of Neurology

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MACMILLAN AND CO., LIMITED
ST. MARTIN'S STREET, LONDON
NEW YORK: THE MACMILLAN COMPANY

Vol. 65. Part 2. 1942 Price 8s. 6d. net. Subscription, 34s. net.

Entered as Second Class Matter, April 24, 1929, at the Post Office at Boston, Mass., under the Act of March 3, 1897 (Sec. 397, P.L. and R.). Printed in Great Britain.

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JUNE, 1942

BRAIN

VOL. 65, PART 2.

STUDIES IN HUMAN VESTIBULAR FUNCTION: I. OBSERVATIONS ON THE DIRECTIONAL PREPONDERANCE ("NYSTAGMUSBEREITSCHAFT") OF CALORIC NYSTAGMUS RESULTING FROM CEREBRAL LESIONS.

BY GERALD FITZGERALD[1] AND C. S. HALLPIKE.

(From the Research Unit, National Hospital, Queen Square, London.)

INTRODUCTION.

IN 1911 Bauer and Leidler described certain changes in post-rotational nystagmus following the removal of one cerebral hemisphere in the rabbit, namely, that the cessation of rotation towards the side of the intact hemisphere, e.g. the right, evoked a much brisker nystagmus than the cessation of rotation in the opposite direction. According to Ewald's Law (1892) the nystagmic responses to cessation of rotation to the right and left are initiated in the main in the left and right labyrinths respectively. This principle was accepted by Bauer and Leidler who interpreted their finding as an exaggeration in the response of the left labyrinth, and were led to the general conclusion that ablation of a cerebral hemisphere gives rise to an increased sensitivity of the homolateral labyrinth. A further investigation was reported in 1923 by Dusser de Barenne and de Kleyn, who were able to confirm the facts as stated by Bauer and Leidler, but refuted the explanation offered. Thus, following the removal of one hemisphere, e.g. the left, there was found as before a marked exaggeration of nystagmus following the cessation of rotation towards the right, so according with Bauer and Leidler's suggestion of an increased sensitivity of the left labyrinth; a suggestion which received further support from the results of hot caloric stimulation of the labyrinths which revealed a marked preponderance of the left reaction.

On repeating the tests, however, with cold stimulation a preponderance was discovered in the reaction of the *right* labyrinth, a finding which clearly disposed of the possibility of any inequality in labyrinthine sensi-

[1] Research Fellow of the National Hospital.

tivity. Since, however, the cessation of rotation to the right and the stimulation of the left and right labyrinths by heat and cold respectively all have a common result in evoking nystagmus to the left, it was made apparent that what in fact had been brought about by extirpation of the left cerebral hemisphere was a central facilitation of induced labyrinthine nystagmus *in a particular direction*, in this case, to the left.

An application of these results to the diagnosis of cerebral lesions was reported in 1928 by de Kleyn and Versteegh. Hot and cold caloric tests were carried out in 36 cases according to the threshold method of Kobrak (1918) and a directional preponderance of the nystagmus was found in 11. No information was, however, given as to the nature or position of the lesions shown by clinical examination, operative or post-mortem findings, except in one instance. In this, a large abscess in the frontal lobe was correlated with a directional preponderance of the caloric nystagmus to the same side.

In the present work an attempt has been made to obtain further evidence of the occurrence in the human subject of directional preponderance of induced labyrinthine nystagmus attributable to cerebral lesions. As will appear, this evidence has been obtained, and a further identification attempted of the locus within the cerebral hemisphere of the nervous mechanism responsible for the reaction in question.

Methods.

The experimental basis of the present investigation has been provided by the caloric tests of Bárány, modified in the light of experience and of certain theoretical considerations. It will be recalled that prior to the publication of Bárány's investigations (1906), vertigo was already a familiar consequence of douching the external auditory meatus with cold water. Bárány rationalized this phenomenon by observing the reversal in direction of the induced nystagmus which resulted alike from certain changes of head position and from the substitution of a hot for the cold stimulus more usually employed. His conclusions were that the physiological effects of thermal stimulation were due to cupular movements brought about by thermally induced convection currents in the endolymph. Subsequent vicissitudes in the status of this theory are worthy of note. In 1918 Kobrak pointed out that a nystagmic response could be elicited by the injection into the external auditory meatus of no more than 5 c.c. of water at 27° C., and considered it impossible that a thermal stimulus of this magnitude could be transmitted to the labyrinth. The fact of such transmission was however clearly established by the thermo-electric measurements of

Schmalz (1931) and of Dohlman (1925), while thermally induced movements of the cupula were finally observed by Steinhausen (1932) in the living pike.

Dohlman's measurements are of particular value in indicating the relative importance of the parts played by the three canals in the make-up of the caloric responses. As might be expected from its superficial position it is found that the wave front of the temperature change first reaches the external canal. With the head inclined backwards by 60°, corresponding to a vertical position of the canal, the temperature gradient along its course is high, as also the speed of the resultant endolymph current. Temperature changes in the vertical canals are smaller and occur later; moreover, the temperature gradients are slight and the endolymph currents in consequence small, particularly in the case of the posterior canal. Whether or not the vertical canals respond at all to caloric irrigation of the meatus cannot yet be stated with certainty, but this is certainly rendered unlikely by the finding of Veits (1928) that no caloric nystagmus can be elicited when the external canal is horizontal, in spite of the fact that this position provides optimal conditions for a temperature gradient along the course of the anterior vertical canal. The particular merit of the caloric test in limiting the stimulus to a single labyrinth is generally conceded, and the further important possibility of limiting the stimulus to a single organ within that labyrinth, namely the external canal, is now clearly imported by the experimental considerations which are outlined above. These considerations have been made the basis of the technique of caloric stimulation devised for the purpose of the present work, and have likewise been applied in the interpretation of the results.

Technique of the caloric tests.—We have put these tests to the particular purpose of revealing and measuring small differences in the nystagmic reactions to left and right evoked by thermal excitation both hot and cold of the external canals; and with this in mind have found it necessary to devote some attention to the details of the technical procedure. It is necessary that the stimuli used should be small in order to restrict excitation to the external canal. Furthermore, it has been found desirable for the purpose of certain comparisons to use hot and cold stimuli which are thermally equidistant from the body temperature. Finally, it has been imperative that the conditions of the test should provide maximum delicacy with a view to revealing small differences in excitability of the reflex mechanisms involved. For this purpose gross stimulations with extremes of temperature are useless. Kobrak's method of graded stimuli using

5 c.c. of water of increasing coldness certainly makes it possible to arrive at a threshold value for the nystagmus-provoking stimulus, and the method has been used by de Kleyn and Versteegh (1928). However, its application is tedious, the threshold value in practice rather diffuse, and the test as prescribed is thus neither very practical nor particularly delicate. Theoretical considerations certainly prompt the expectation that greater precision would be attainable by measurement of one or more attributes of the responses to some suitably graded supra-liminal stimulus, and in this case we have followed the usual practice in selecting the duration of the nystagmus as the attribute to be measured. A decision as to the best values of temperature and duration of the thermal stimuli has been a matter of some difficulty. Preliminary trials were made upon some forty normal individuals and upon an equal number with vestibular abnormalities differing widely in character and degree. Various combinations of the time and temperature components of the thermal stimuli were tried and upon this basis a satisfactory technique was eventually standardized. Its general lines follow those recommended by Grahe (1920, 1921) and by Vogel (1929), who use water at 17° or 27° and 47° C. in comparatively small quantities. The latter temperature is ill tolerated on occasions and we therefore prefer the use of water at 30° and 44° C. allowed to flow freely for forty seconds. Accurate temperature adjustment is facilitated by the comparatively large quantity of water so used, while its rapid flow minimizes error due to misdirecting the stream within the meatus. The close approximation of the temperatures chosen to 37° C. ensures that the stimuli are kept physiologically small. It is right to say that the technique thus evolved introduces no new matter of principle. It is to be regarded as novel only in so far as it represents a calculated endeavour to push to its limits the resolving power of the caloric tests. In this it has proved very successful, at any rate in our hands. Very small differences of response duration have been found measurable and can be reproduced on repetition. Provided always that such differences go to make up one of a few specific disturbances in the pattern of the four responses little difficulty has arisen in estimating their significance. In this way the scope of the tests has been considerably extended. By this is meant that the technique has greatly facilitated the recognition of abnormal reactions in patients with collateral evidence of vestibular disease; and that further it has made possible a much closer analysis of these abnormalities, both qualitative and quantitative, than would otherwise be attainable. The tests are not easy to carry out, and require considerable practice and attention to detail.

Procedure.—A two-pint metal douche can is filled from hot and cold taps. The temperature is taken with a thermometer reading to 0·1° C. mounted upon a perforated wooden plunger used for mixing. The temperature is adjusted roughly to about 1° C. above that required, and a fine adjustment is then carried out by running cold water round the base of the container while keeping the contents constantly mixed. The water is led to the ear through a rubber tube with a pressure head of about 2 ft. The nozzle used has an internal diameter of 4 mm., and the stream is a fairly heavy one, some 8 ozs. being delivered during the stimulus time of forty seconds. The feed tube is run off before starting the irrigation, and the stream is directed towards the posterior wall of the meatus. The time interval between the temperature adjustment of the water and the commencement of the irrigation is about fifteen seconds and is kept constant within a few seconds.

The nystagmus provoked by these means in a normal individual lasts for about one and a half to two and a half minutes, is nearly always easy to observe, and very seldom accompanied by nausea or severe vertigo. Accuracy in estimating the duration of the nystagmus depends greatly upon the method of its observation. Bartels glasses for the abolition of fixation have been frequently recommended. We have preferred not to use them. They prolong the reaction and in our experience rather diffuse its end-point. In addition, their use in patients with spontaneous nystagmus may be found to complicate measurements by inducing ocular deviations. We have found it of advantage to confine our observations to nystagmus occurring in the straight ahead position of the eyes, so-called second degree nystagmus, accompanied by voluntary fixation. The patient lies comfortably on a couch with his head raised about 30° above the horizontal, thus bringing the external canal into its maximum position for caloric excitation. His gaze is fixed straight ahead upon a convenient mark on the ceiling. The nystagmus is watched by two observers stationed on each side of the couch and using light reflected from head mirrors, from a source above and behind the patient's head, care being taken not to interrupt the patient's line of fixation. The observations are made from a distance of about 12 in., and are discontinuous in the early stages of the reaction in order to avoid fatigue. The time interval selected for measurement extends from the application of the stimulus to the end of the nystagmic response, and the measurement is made with a stop watch. Our choice of this starting point in place of the more usually selected onset of the nystagmus is perhaps worthy of remark. With the stimulus conditions

specified, this latter point is often found to occur at or shortly preceding the end of the irrigation, which renders its accurate observation a matter of some difficulty. Moreover, Dohlman's measurements have shown that much the greater part of the latent period of caloric nystagmus is made up of the transmission time of the thermal wave through the bony pathway to the labyrinth, and that significant variations in this transmission time as between the two ears of a given individual are improbable. Furthermore, the absolute value and possible range of variation of the true latent period of the canal organ is much too small to be considered within the range of the present observational method. For these reasons the selection of the time interval specified as a measure of nystagmus-strength would appear to be well justified from the view points of both theory and technical facility. Its description as "nystagmus duration" is clearly wanting in accuracy, but for the purposes of convenience it will be so described in the following sections of this paper. As already stated, attention is principally devoted in these measurements to the duration of the nystagmic response. Nevertheless a general impression of its briskness is often useful. Thus a small difference in duration between two responses is always found to be significant if associated with an obvious difference in their briskness. The time taken for a single test is about four minutes. Each subject requires 4 such tests with an interval between tests of at least five minutes. The tests are most conveniently carried out upon batches of three or four subjects, who are tested in turn. Under favourable conditions of activity and co-operation 4 subjects can be completely examined within an hour.

Results.

A.—Normal.

Typical results of the caloric tests carried out according to the technique described in a normal individual are shown below in a convenient diagrammatic form (fig. 1). Each continuous line represents a three-minute

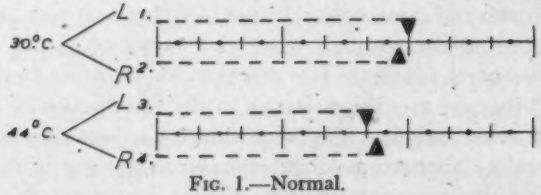


Fig. 1.—Normal.

period, sub-divided into intervals of minutes, twenty seconds and ten seconds. The reactions of the left and right ears are denoted by L. and

R., while the stimulus time extends in all over the first forty seconds. The interrupted line - - - denotes the nystagmus duration.[1] As stated, the set of reactions shown is typical of most normal individuals. An idea of the normal limits of the test results was obtained from the findings in fifty individuals between the ages of 20 and 55 with normal hearing and without symptomatic or other evidence of vestibular disorder. In 80 per cent. of these the duration of the cold reactions varied between 1.30 and 2.10 minutes, with extremes in the remaining 20 per cent. of 1.20 to 2.40 minutes. In 80 per cent. the cold reactions were in excess of the hot, usually by five to fifteen seconds, and with a maximum difference of thirty seconds. (It is worthy of comment that both Grahe (1932) and de Nó (1936) have noted a similar preponderance of the cold responses with stimulus temperatures of 27° and 47° C.) In 10 per cent. the cold and hot reactions were approximately equal, and in 10 per cent. the hot reactions exceeded the cold with a maximum difference of fifteen seconds. In 80 per cent. the cold reactions of the two ears showed a difference of five seconds or less. In 10 per cent. this difference was ten seconds, and twenty to twenty-five seconds in the remaining 10 per cent. Differences of a similar order were observed in the hot reactions. In addition, these tests have been repeated in a number of normal individuals at intervals varying between two hours and two months. No significant variations have been encountered.

These preliminary observations defined the approximate limits of normal variation both in the magnitude and mutual relationship of the caloric response. Whilst in accordance with all observations since the time of Bárány, the normal limits in the general magnitude of the responses are shown to be fairly wide, it is fortunately possible to add that such variations have been proven to bear but little upon the diagnostic worth of the tests. The normal limits of variation in the mutual relationship of the four responses is much less. Certain changes in this relationship have been observed in association with well attested lesions of the labyrinth and its central connections and can now be briefly described. They are clear-cut in type and of high diagnostic significance.

B.—Pathological.

As shown in the test diagram (fig. 1), the four reactions take the form of a rather characteristic four-element pattern with the two cold reactions roughly equal and rather in excess of the two hot reactions, which again

[1] The reactions will be further referred to in the text by the numbers 1, 2, 3 and 4 from above downwards as they appear in the diagram.

are roughly equal. Disturbances of this pattern may take one of the three following forms, each with a particular diagnostic significance.

(1) *Disturbance in the relationship of the nystagmus-to-the-right reactions (reactions 1 and 4) to the nystagmus-to-the-left reactions (reactions 2 and 3).*—Disturbances of this type are due to directional preponderance, and examples are given in the following figures. Fig. 2 shows

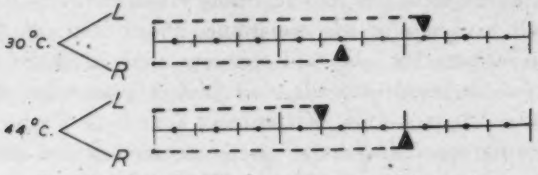


FIG. 2.—Directional preponderance to the right.

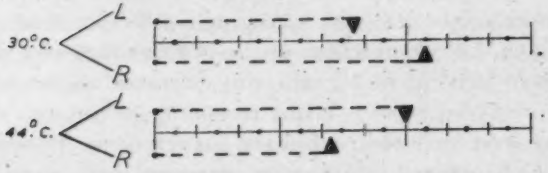


FIG. 3.—Directional preponderance to the left.

directional preponderance to the right, i.e. exaggeration of reactions 1 and 4 with respect to reactions 2 and 3. Fig. 3 shows directional preponderance to the left, i.e., exaggeration of reactions 2 and 3 with respect to reactions 1 and 4. It is necessary to emphasize that within the four-element pattern typical of either variety of directional preponderance each ear exhibits a specific type of alteration of its own reactions. Thus in the case of a preponderance to the right (fig. 2), it will be observed that the normal relationship of the cold to hot reactions of the left ear is altered in favour of the cold, and of the right ear in favour of the hot. *In other words, the diagnosis of a directional preponderance is usually dependent upon two independent but complementary clues, each provided by the reactions of one ear.* It is of particular importance to add that when one such clue is eliminated, as may result from the destruction of one labyrinth, the occurrence of a directional preponderance may still be correctly deduced from a characteristic alteration in the reactions of the opposite ear alone. This type of situation is dealt with in detail in the succeeding paper.

(2) *Disturbance in the relationship of the cold and hot reactions of the left ear (reactions 1 and 3) to the cold and hot reactions of the right ear (reactions 2 and 4).*—Disturbances of this type are due to paresis of the

external canal of the ear exhibiting the lesser responses and will be referred to as canal paresis. Examples are given in the following figures. Fig. 4

FIG. 4.—Left canal paresis.

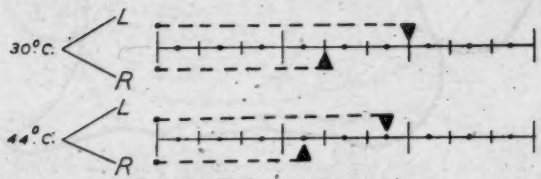


FIG. 5.—Right canal paresis.

shows a left canal paresis, i.e. diminution of reactions 1 and 3 with respect to reactions 2 and 4. Fig. 5 shows a right canal paresis, i.e. diminution of reactions 2 and 4 with respect to reactions 1 and 3.

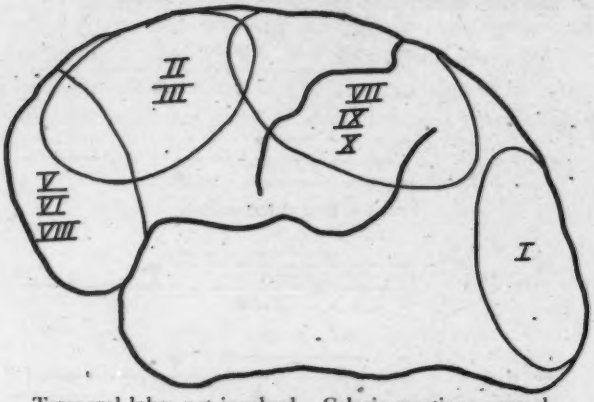
(3) *More complex changes in reaction pattern which analysis has shown to arise from a variety of combinations of directional preponderance and canal paresis.* Disturbances of this kind are described as being of the "combined type" and will be more fully discussed in a later paper which deals with the clinical features of "Ménière's" disease.

The present paper deals exclusively with directional preponderance occurring in association with lesions of the human cerebrum. The succeeding paper deals mainly with directional preponderance brought about by unilateral labyrinth destruction in the human subject, and to a lesser extent with the subject of canal paresis, while a third paper is devoted to further discussion of all three types of disturbance in the reaction patterns which are found to occur in the natural course of the labyrinthine disorder known as "Ménière's" disease.

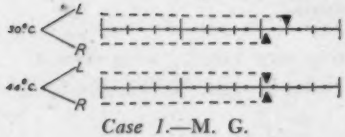
Directional Preponderance Due to Cerebral Lesions.

Material and results.—Caloric tests were carried out upon sixteen inpatients at the National Hospital, Queen Square, and upon four patients under the care of Mr. Wylie McKissock at Leavesden Emergency Hospital. In all of these the diagnosis and localization of a cerebral lesion had been well established either on clinical grounds alone or supported by the direct evidence of operative or post-mortem findings. For the purpose of descrip-

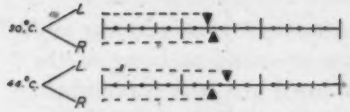
TABLE I.



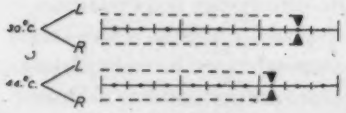
Temporal lobes not involved. Caloric reactions normal.



Case 1.—M. G.

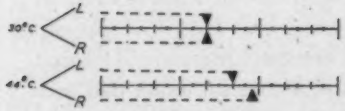


Case 2.—D. F.

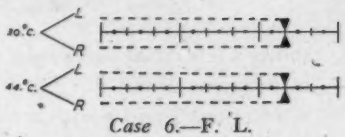


Case 3.—F. F.

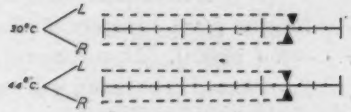
Case 4.—K. A.



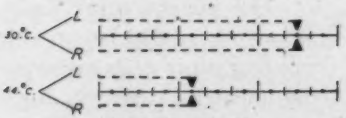
Case 5.—T. H.



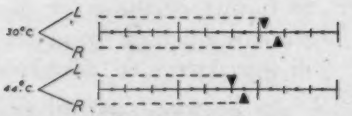
Case 6.—F. L.



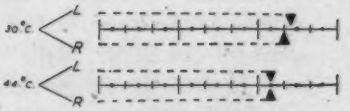
Case 7.—A. L.



Case 8.—G. P.

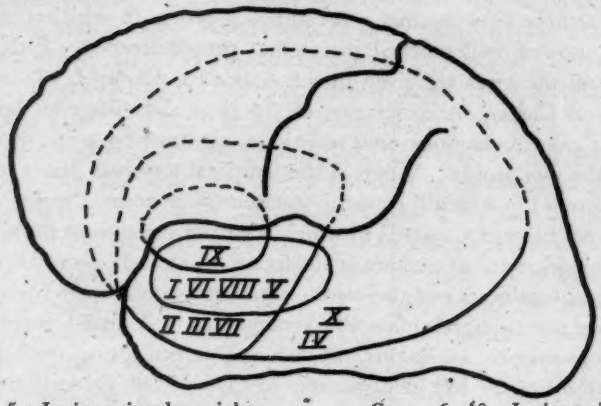


Case 9.—A. S.

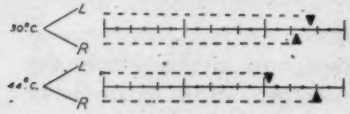


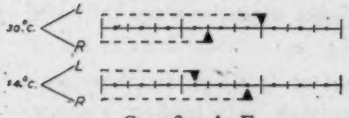
Case 10.—S. T.

TABLE II.



Cases 1 - 5.—Lesions involve right temporal lobe. Directional preponderance of caloric nystagmus to the right.



Case 1.—E. D.

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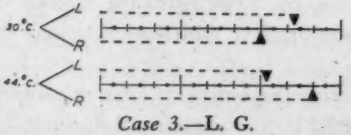

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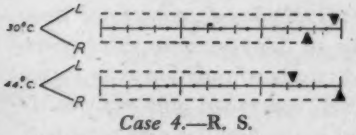
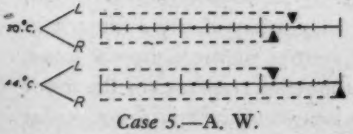
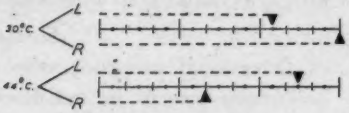


Case 4.—R. S.

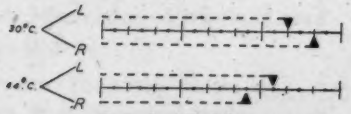


Case 5.—A. W.

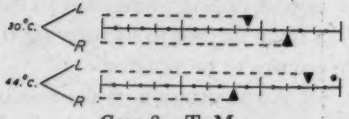
Cases 6 - 10.—Lesions involve left temporal lobe. Directional preponderance of caloric nystagmus to the left.



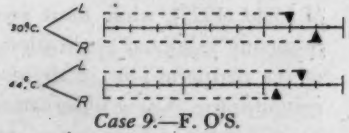
Case 6.—A. F.



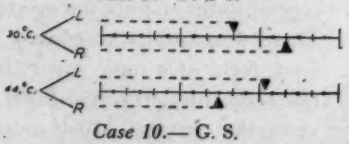
Case 7.—F. M.



Case 8.—T. M.



Case 9.—F. O'S.



Case 10.— G. S.

tion the cases are divided into two groups. Firstly, a group in which the caloric reactions were normal. Secondly, a group in which the caloric reactions showed well marked directional preponderance. Full clinical details of all the cases are given in the Appendix (Group I, 10 Cases, and Group II, 10 Cases). A correlation of the clinical findings in these cases with their caloric reactions now reveals an outstanding point of contrast between the two groups. Whereas the temporal lobe was intact in all ten cases of Group I in which the caloric reactions were normal, it was involved in all the ten cases of Group II in which the caloric reactions showed directional preponderance to the side of the lesion. A clearer appreciation of the neurological significance of the caloric reactions is obtainable from a study of the data more diagrammatically arranged as in Tables I and II.

For convenience, all lesions are depicted as being projected upon the lateral surface of the left hemisphere. In cases I-V of Table II the lesions involved the right temporal lobe with directional preponderance of caloric nystagmus to the right. In cases VI-X the left temporal lobe was involved with directional preponderance of caloric nystagmus to the left.

Summary of Results.

Directional preponderance of caloric nystagmus to the side of the lesion was present in ten cases of lesions localized within or involving the temporal lobe. It was absent in ten other cases in which lesions were localized to portions of the cerebrum other than the temporal lobes.

Discussion.

The results described confirm the findings of de Kleyn and Versteegh that cerebral lesions in man, as in certain animals, may lead to exaggeration of caloric nystagmus to the side of the lesion. They carry the matter a stage further in identifying the region of the brain in which such lesions require to be situated.

An association of the vestibular system with the temporal lobe, at any rate upon the sensory side, is already supported by the anatomical findings of Held (1922), while more recently Spiegel (1932) has demonstrated that following localized application of strychnine to the postero-superior parts of the temporal lobe in the dog and cat labyrinth stimulation may cause convulsions. These observations are, however, concerned only with corticopetal fibres and are not essentially involved in the findings now recorded. These we consider to convey a very clear suggestion of the existence in some form of a tonic controlling action of centres in the temporal lobes, exercised through *corticofugal* fibres, upon the reflex responses of the lower vestibular centres. Much more is of course known of the control of ocular

movements by tonic impulses which proceed from the labyrinths by way of the vestibular nuclei. This subject is dealt with in some detail in the discussion which follows the succeeding paper to which we think it profitable to postpone the further consideration of the possible nervous mechanism within the brain stem of the tonic impulses from the temporal lobes with which we are now concerned. Although the present paper deals only with the occurrence of directional preponderance of caloric nystagmus due to lesions of the temporal cortex, it may be added that the same phenomenon has been observed in association with a number of lesions at rather lower levels which may be supposed to interrupt the pathway of these cortico-fugal fibres. It is possible that the diagnostic value of directional preponderance of caloric nystagmus, as elicited by the technique described, may prove to be considerable. The right temporal lobe is a notoriously silent zone of the cortex, and in this respect Collier (1929) has put it on a footing with the prefrontal areas. Although much attention has been paid since Cushing's paper in 1921 to the localizing value in temporal lobe lesions of disturbances in the visual fields it should be noted that Kolodny (1928) in his analysis of the clinical findings in temporal lobe tumours at the National Hospital found such disturbances in only 18·5 per cent. of his cases. On the other hand, directional preponderance of caloric nystagmus has been demonstrable in all of our cases in which a lesion of the temporal lobe could be regarded as established by the clinical, operative or post-mortem findings.

SUMMARY.

(1) A description is given of the discovery by de Barenne and de Kleyn of the phenomenon of directional preponderance of induced labyrinthine nystagmus ("Nystagmusbereitschaft") brought about in rabbits by the removal of one cerebral hemisphere.

(2) Attention is drawn to the later discovery by de Kleyn and Versteegh of the same phenomenon in the human subject occurring in association with cerebral lesions.

(3) The physical basis of the caloric tests is discussed, and improvements are described in the technique of their application.

(4) As so improved the tests have been systematically applied to normal human subjects and to a number of patients in whom the existence and localization of a variety of cerebral lesions had been established by clinical, operative or post-mortem findings.

(5) In all of ten cases with lesions of one temporal lobe directional preponderance of caloric nystagmus was observed to the side of the lesion.

In all of ten cases with lesions which did not involve the temporal lobes the caloric reactions were normal.

(6) The findings are therefore considered to confirm and extend the observations of de Kleyn and Versteegh.

(7) Their theoretical and diagnostic implications are briefly discussed.

APPENDIX.

Group I. Normal Caloric Reactions.

Case 1.—M. G., female, aged 43, admitted under the care of Dr. Gordon Holmes on June 26, 1941, with a history of left supraorbital headaches for the previous ten years; these were accompanied by flashes of light in the left eye. Headaches occurred in the morning accompanied by nausea and vomiting, and lasted for a day. These headaches increased in severity until a year before admission, when the patient was prescribed glasses. They had not since returned in this form. About four months later she began to see double and to have occipital headaches unaccompanied by nausea or vomiting; these woke her in the morning and lasted for about an hour. For about the same period she had been aware of a slight pulsating tinnitus in the left ear.

On examination the patient was drowsy.

Cranial nerves: Bilateral papilloedema. Right homonymous hemianopia to a third degree white object with sparing of the fixation point. There was a questionable right facial weakness.

Motor system: The tendon and superficial reflexes were within normal limits and equal. The sensory examination disclosed a slight loss to two point discrimination on the right hand.

Investigations: X-rays of skull gave evidence of long standing increase of pressure. Cerebrospinal fluid was at a pressure of 90 mm. of water. Ventriculography failed to fill the left ventricle with air.

On operation a left parietal flap was turned down and a meningioma invading the parieto-occipital lobe about the size of an orange encountered. It was successfully removed.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 2.—D. F., male, aged 30, admitted under the care of Dr. F. M. R. Walshe on December 2, 1941, complaining of headaches of six weeks duration. These headaches had not increased in severity or frequency, but were present when he woke in the morning; they were not accompanied by nausea, vomiting or giddiness. They were mainly sub-occipital in position and were felt as a dull ache. For about one month he had suffered from considerable lassitude.

On examination the patient was co-operative. There was no speech defect. Both fundi showed evidence of early swelling.

Motor system: Nothing else abnormal was detected on physical examination except a slight increase in tendon reflexes on the right side.

Investigations: On ventriculography some generalized dilatation with displacement to the right of the ventricular system. There was deficient filling of the body and anterior horn of the left ventricle. A diagnosis of left frontal neoplasm was made.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 3.—F. F., male, aged 53, admitted under the care of Dr. Gordon Holmes

with a history of being well until five weeks previously when he began to complain of a dull aching headache. He had vomited occasionally in the mornings. A fortnight later he seemed confused and unable to concentrate, while the headache had increased in severity.

On examination the patient was confused, apathetic and un-co-operative. He appeared to understand speech, but was unwilling to carry out simple instructions. He could name objects. He was incontinent of urine.

Cranial nerves: Discs normal in colour with evidence of early papilœdema. There was a questionable right lower facial weakness on voluntary movement.

Motor system: The tone and power appeared within normal limits with co-ordination good. Tendon reflexes were uniformly present and equal. Bilateral extensor plantar responses.

Investigations: Skull and chest X-rays were normal. Cerebrospinal fluid was under pressure of 250 mm. of water with a protein content of 130 mg.%. A diagnosis of left frontal glioblastoma involving the corpus callosum and right frontal lobe was made. The patient died within the next two weeks while in hospital.

Auditory function: As far as could be tested, equal and normal. Tympanic membranes normal.

Case 4.—K. A., male, aged 16, admitted under the care of Dr. J. St. C. Elkington on March 31, 1941, with a three years' history of attacks of unconsciousness preceded by a pain over the left eye. The pain lasted for about half an hour, and on two occasions was followed by loss of consciousness. It was said that before the loss of consciousness his right eye became "staring." During the attack his left leg "shook." He had lost consciousness only twice. On other occasions he had apparently wandered around for an hour or two and had subsequently no memory covering the period. For three months he has had severe bifrontal headaches, unaccompanied by nausea or vomiting.

On examination he appeared to be a dull youth.

Motor system: Within normal limits except for slight dysdiadokokinesia of both arms, more marked on the left side than the right. There was a slightly deficient power of dorsiflexion of the left foot.

Investigations: Cerebrospinal fluid was under normal pressure and was normal in constituents. Cisternal encephalogram gave a picture suggestive of a septum pellucidum cyst. On ventriculography the two lateral ventricles were found widely separated and very much enlarged. The third ventricle was dilated.

On operation, a right parietal osteoplastic flap was turned down. The corpus callosum could not be easily identified, as a large cystic swelling protruded upwards from its posterior end.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 5.—T. H., female, aged 60, had been an in-patient under the care of Dr. Hinds Howell in August, 1935, when a large left frontal meningioma weighing 60 grm. was removed. Following the operation the patient improved remarkably and was discharged free from abnormal physical signs. She remained well until two months before being again admitted to hospital on Febrary 23, 1942. She then complained of slight frontal headaches with a dimness of vision in the left eye. This had commenced two months before and vision had progressively deteriorated during the intervening period.

On examination the patient, though verbose, appeared normal mentally.

Cranial nerves: There was left anosmia. Right visual acuity, $\frac{6}{6}$; left visual acuity, perception of movement of large objects. The left pupil reacts sluggishly

to direct light, with brisk response on convergence.

Motor system: Nothing else abnormal was detected on physical examination except a right equivocal plantar response.

Investigations: Skull X-rays showed a degree of hyperostosis in the region of the left orbital plate and of the lesser wing of the sphenoid. On lumbar puncture the cerebrospinal fluid was normal in constituents and under normal pressure. A diagnosis was made of a recurrence of a left frontal meningioma pressing on the left optic nerve.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 6.—F. L., male, aged 32, admitted under the care of Dr. George Riddoch on April 20, 1941. The patient had enjoyed good health until April, 1940, when he suddenly lost consciousness and "did not remember anything for twenty-four hours" when he came round with a severe throbbing occipital headache. He remained well until December, 1940, when he had an attack of nausea and vomiting and woke up next morning with a headache similar to that which he had previously experienced. The headaches persisted, and he has had five more attacks of nausea and vomiting. In February 1941 he noticed a curious sensation in his left eye, and since then his vision had deteriorated.

On examination the patient was alert and co-operative.

Cranial nerves: Bilateral papillœdema with fine hæmorrhages and exudates. Some weakness of right lower face.

Motor system: The right arm and leg were a little more flaccid than the left, and co-ordination was not so good on the right side. Reflexes brisk and equal.

Investigations: On ventriculography a moderate hydrocephalus was noted, with a displacement to the right by a left frontal tumour far forward.

On operation a cystic astrocytoma was found occupying the anterior pole of the left hemisphere.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 7.—A. L., male, aged 48, admitted on March 24, 1942, under the care of Mr. Wylie McKissock at Leavesden Emergency Hospital. Two months previously the patient had begun to complain of frontal headaches which had in the interval increased in severity. They were unassociated with nausea or vomiting. Further details were difficult to obtain as the patient was inattentive, disoriented as to time and space and his memory was grossly deficient. He lacked insight. During the examination he yawned repeatedly but did not appear very drowsy. His narrative was punctuated with irrelevant flippancies which he exchanged with the patients in the ward. He was disinclined to carry out simple tests, though there was no evidence of apraxia, agnosia or aphasia.

Cranial nerves: Well-marked papillœdema with hæmorrhagic exudates. Very early paresis of voluntary movement of the lower half of the right face.

Motor system: Slightly brisker tendon reflexes were elicited from the right side, but apart from these nothing abnormal was detected.

Investigations: Cerebrospinal fluid was under a pressure of 280 mm. of water but was normal in constituents. Ventriculogram showed a shift of the whole ventricular system towards the right side. This displacement was about equally marked on the anterior and posterior ends of the system.

The patient died on March 30, 1942, and on autopsy secondary carcinomatous deposits from a primary site in the bronchus were found in the left frontal and parietal lobes.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 8.—G. P., male, aged 27, admitted under the care of Dr. Hinds Howell on February 24, 1942. The patient had been previously investigated on November 8, 1939, for occipital headaches, generalized epileptiform convulsions and loss of vision in the right eye. A strongly positive Wassermann in the cerebrospinal fluid and blood was found on this occasion. The patient was discharged much improved following a course of specific therapy. He was advised to keep in touch with the hospital but failed to do so. When admitted for the second time he stated that he had remained well until a few months before, when the epileptic attacks recommenced. About the same time vision in the left eye began to deteriorate. Severe occipital headaches commenced two weeks before admission.

On examination the patient was co-operative.

Cranial nerves: Bilateral anosmia with bilateral consecutive optic atrophy, the right disc being uniformly more pale than the left. Visual acuity in the left eye was reduced to perception of light in the temporal half, while vision in the right eye was less than $\frac{6}{60}$. Visual acuity was too poor to estimate field defect accurately.

Investigations: On lumbar puncture the cerebrospinal fluid was under a pressure of 300 mm. + of water, but was normal in constituents, including a negative Wassermann. On ventriculogram, X-ray pictures showed moderate dilatation of the lateral and 3rd ventricles with a shift to the right of the left frontal region.

On operation a large hard tumour was found at the tip of the left frontal pole attached to the dura and the base. The patient's condition deteriorated rapidly following operation, and at post-mortem the presence of a large meningioma attached to the anterior part of the left frontal lobe was confirmed.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 9.—A. S., male, aged 39, admitted under the care of Dr. E. A. Carmichael on March 3, 1942, with a history of increasing headaches for one month. These headaches, which were located to the right side of the head, had become almost constant for a fortnight. A week before, he had begun to vomit, and this had persisted.

On examination the patient appeared to be in considerable pain, and though co-operative, was rather apathetic. He stated that he did not feel drowsy.

Motor system: Apart from diminished abdominal reflexes on the left side with slightly exaggerated tendon reflexes on the same side nothing abnormal was detected.

Sensation: There appeared to be diminished appreciation to all modalities on the left side.

Investigations: A ventriculogram performed on March 11, 1942, gave a picture suggestive of fronto-parietal neoplasm.

On operation this was confirmed, when a fronto-parietal flap was turned down and a large tumour was noted in this region. The patient died.

On post-mortem "a large glioma was present in the fronto-parietal region extending across the mid-line in the anterior part of the corpus callosum."

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 10.—S. T., male, aged 38, admitted under the care of Dr. George Riddoch with a history of epileptiform seizures for six years. These commenced with "pins and needles" sensation in the left foot, spreading up the left leg to the left half

of the body. He then lost consciousness. These attacks had recently increased in severity and number.

On examination the patient was intelligent and co-operative.

Motor system: The tendon reflexes from the left lower limb were brisker than in the right, with an extensor plantar response from the left sole.

Investigations: Skull X-rays showed a calcified lobulated nodule in the right motor cortex. On lumbar puncture the cerebrospinal fluid was normal in constituents and under normal pressure.

On operation a right parietal osteoplastic flap was turned down and a considerable degree of cerebral softening found, extending from the frontal to the parietal cortex.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

GROUP II. DIRECTIONAL PREPONDERANCE OF CALORIC NYSTAGMUS TO SIDE OF LESION.

Case 1.—E. D., female, aged 57, admitted to Leavesden Emergency Hospital on March 29, 1942, under the care of Mr. Wylie McKissock. The patient had been in good health except for "migrainous headaches" until July, 1941. These headaches were occipital in position, accompanied by nausea, but not by visual hallucinations. They were of twenty-seven years' standing. In July, 1941, for the first time she began to notice bright lights "white and red" playing about the left side of her field of vision during the course of a severe headache. Since then she had twice lost consciousness. There was no adequate description available of the patient's condition while unconscious. Since Christmas, 1941, the character and periodicity of the headaches had changed. They had become constant, vertical in position, and increased by any movement such as stooping, bending or coughing. They were worse on waking, but not associated with nausea.

On examination the patient was intelligent and co-operative. There was a left temporal homonymous hemianopia with a sparing of the fixation point.

Motor system: Physical signs of a slight left hemiplegia with deficient abdominal responses on the left side.

Sensory system: Some impairment of a doubtful character to two point testing over the left hand.

Investigations: Skull X-rays normal. Ventriculography showed filling only of the left lateral ventricle with a displacement towards the left side.

On operation following a right temporal flap a needle inserted into the right temporal lobe encountered firm resistance at a depth of 5 cm. In view of the patient's age and general condition and the evident size of the neoplasm, no effort was made to remove it.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 2.—A. E., female, aged 44, admitted under the care of Dr. E. A. Carmichael on October 22, 1940, with a history of generalized epileptiform convulsions during the previous six years. For three months before admission she had had severe headaches and morning vomiting. The epileptiform seizures had been increasing in number. For the previous three months she had changed in character, becoming a docile dull woman.

On examination the patient co-operated, and showed no aphasic or apraxic features.

Cranial nerves: Bilateral papilloedema, fine hæmorrhages. Some defective emotional movement of the left lower face with slight deviation of the tongue to the left.

Motor system: There was a coarse tremor of both outstretched hands, with uniformly exaggerated tendon reflexes and bilateral extensor plantar responses.

Investigations: The cerebrospinal fluid was under 300 mm. pressure of water but was normal in content. A ventriculogram showed a displaced ventricular system to the left.

Post-mortem findings: A right fronto-temporal neoplasm was confirmed at post mortem, the findings being "a large subcortical glioma extending from the frontal lobe to the fronto-parietal and fronto-temporal regions."

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 3.—L. G., male, aged 11, admitted under the care of Dr. Purdon Martin on March 18, 1939, with a history of tenderness of the forehead since December 5, 1938. Shortly after this he was examined in the local hospital and was said to have "pyrexia, neck rigidity and a positive Kernig's sign." There was evidence of consolidation at the right base. Within the next three weeks he had a convulsion, following which his left arm became weak. This was followed by weakness of the left leg.

On examination he did not complain of headaches, was not drowsy and co-operated fully.

Cranial nerves: Bilateral papillœdema with left lower quadrantic hemianopia to a 3 mm. white object. Weakness of the left lower face.

Motor system: Physical signs of a left hemiplegia with exaggerated tendon reflexes, absent left abdominal reflexes and a left extensor plantar response.

Sensation: Diminution of two point discrimination over the left hand.

Investigations: On lumbar puncture the cerebrospinal fluid was at a pressure of 300 mm. of water but was normal in content.

Operation: On April 17, 1939, a right parietal flap was turned down. In successive stages necessitating further bone removal, a large parieto-temporal abscess was aspirated. The patient made a slow recovery, and when seen on June 30, 1941, had residual signs of a left hemiplegia with left homonymous hemianopia not involving the fixation point.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 4.—R. S., male, aged 37, admitted under the care of Dr. E. A. Carmichael on March 10, 1942, with a history that three months previously he had been hit on the head by a heavy baulk of wood. Following this he was unconscious for three to four days, and on recovery of consciousness he found that he could not use his left arm and leg. Since then his left leg had steadily improved, but not so the arm, which he was still unable to move.

On examination the patient proved co-operative and intelligent.

Cranial nerves: A left superior quadrantic hemianopia could be demonstrated. There was a marked weakness of voluntary movement of the left lower face with deficient closure of the left eye.

Motor system: Signs of a gross left spastic hemiplegia involving the arm more than the leg were demonstrable with exaggerated tendon reflexes, diminished abdominals and an extensor plantar response on the left side. All modalities of sensation were impaired on the left side of the body and head.

A diagnosis of right middle cerebral arterial thrombosis was made.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 5.—A. W., female, aged 32, admitted to Leavesden Emergency Hospital on April 18, 1942, under the care of Mr. Wylie McKissock. For nine weeks the patient had been suffering from increasingly severe headache and vomiting. Over the same period the patient's memory had remarkably deteriorated.

On examination she was apathetic, but to a mild degree resented examination.

Cranial nerves: Bilateral early papilloedema. Slightly deficient movements of the right half of the face.

Motor system: Nothing abnormal detected except that the left upper abdominals tired more easily.

Investigations: Skull X-rays were normal. Ventriculogram showed deficient filling of the right lateral ventricle with displacement towards the left side.

On examination through a burr hole an irregular resistance was encountered towards the tip of the right temporal lobe from which yellowish fluid and material was aspirated. This was confirmed as a gliomatous cystic growth.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 6.—A. F., female, aged 60, admitted under the care of Dr. F. M. R. Walshe on January 28, 1942. The patient was unable to give an adequate history, but it appeared that until six months previously she seemed in good health. Then she had begun to suffer from attacks of giddiness, nausea and vomiting unassociated with tinnitus or deafness. She did not complain of headache at this time. Over the succeeding months her memory had become poor, and she became unable to concentrate. Within the six weeks before admission her right arm had grown slowly weak and her speech had become unintelligible.

On examination the patient appeared to have lost some weight but was not cachectic. There was a gross defect of comprehension, with an unintelligible jargon aphasia.

Cranial nerves: Within normal limits. Fields: Right homonymous hemianopia. Right lower facial palsy of the upper motor type.

Motor system: Complete loss of voluntary power in the right arm with a moderate degree of weakness of the right lower limb. No change in tone on either side. Tendon reflexes were exaggerated on the right side, and this was most marked in the upper limb. Right extensor plantar response. A diagnosis of left temporal glioma was made on consideration of the jargon aphasia, homonymous hemianopia and maximum motor involvement of the upper limb.

Auditory function: As far as could be tested, normal. Tympanic membranes normal.

Case 7.—F. M., female, aged 49, admitted under the care of Dr. Gordon Holmes on March 17, 1941. The patient had a three years' history of headaches which were occasionally very severe, but more commonly a constant dull left frontal ache. Shortly before admission these headaches had been accompanied by nausea. Two years before she had woken to find that her tongue and mouth seemed to be "tied in a ball." Her face was pulled to the right and her eyes diverged in the same direction. No loss of consciousness, no receptive defect, though she could not speak. This lasted about a quarter of an hour. Following it she could not converse easily for five days, and the right side of her face felt "peculiar" for a week. A number of similar attacks had occurred within the next two years. Some of these were severe, but others very slight. For almost a year she has had numerous little spells in which for a few moments she felt a choking sensation and a trembling of the hands and right leg. For a little while following these she has found it

difficult to remember words,and writing was also sometimes difficult. She had been aware of a slight tinnitus in the left ear for about one year. Nothing relevant in family or previous history.

On examination there was a demonstrable hypalgesia and hypæsthesia over the right trigeminal distribution, with a corneal reflex depressed on the same side. Some deficiency in voluntary movement of the right face. Emotional movement normal. The tendon reflexes were uniformly brisk with a right extensor plantar response. The abdominal reflexes could be more easily tired by repetition on the right side. The hypalgesia and hypæsthesia noted over the right 5th nerve distribution extended on to the right arm. Two point discrimination, joint function and stereognosis were normal.

Investigations: The cerebrospinal fluid was under 200 mm. pressure of water and contained 80 mg. per cent. of protein. On ventriculography, the ventricular system was displaced to the right, the displacement of the roof being more pronounced than that of the floor. The final diagnosis confirmed by ventriculography and burr hole was of a large infiltrating glioma of the left hemisphere. This glioma extended into Broca's Area and the temporal lobe.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Case 8.—T. M., male, aged 35, admitted on November 25, 1941, to Leavesden Emergency Hospital under the care of Mr. Wylie McKissock. The patient had been in good health until November, 1941, when he woke up feeling "dizzy" and with a severe headache. Since then the headache had increased in severity and frequency. Over the same period the patient's mentality had deteriorated.

On examination he was unable to give an account of the development of his condition or to answer simple direct questions. There was a gross jargon aphasia. He could not carry out instructions nor recognize simple objects.

Cranial nerves: Bilateral papillœdema. Marked lower right facial weakness on voluntary movement.

Motor system: Slight right hemiplegia affecting the arm more than the leg. The tendon reflexes were brisker on the right than on the left side, with deficient abdominal responses on this side, and an equivocal plantar response.

Investigations: Skull X-rays were normal. Ventriculography gave the appearance of a large space-occupying lesion in the left temporal lobe.

On operation this was confirmed when, following a left temporal flap, an incision was made into the superior temporal convolution and a ragged reddish gliomatous cystic cavity exposed.

Auditory function: Tympanic membranes normal. Hearing: As far as could be tested, normal.

Case 9.—F. O'S., male, aged 50, admitted under the care of Dr. F. M. R. Walshe on April 11, 1942. For about ten years the patient had had attacks of right facial spasm, all of which were without loss of consciousness. They commenced with a blinking movement of the right eyelid after which the right half of the face went into spasm. This lasted for between ten seconds and one minute. During the attack he could not speak, but immediately following it he was able to do so. The attacks had grown very much more frequent within the previous year, and had become almost continuous.

On examination the patient proved intelligent and co-operative, without evidence of motor or sensory aphasia. The right nasolabial fold was poorly marked, and voluntary movement of the right lower face was diminished. At many times within

the space of an hour the right face was disturbed by twitching, writhing motions. This movement appeared to involve the lower half of the face and tongue, and spread to a certain extent into the neck. During the attack the patient was unable to speak but was quite conscious.

Investigations: Skull X-rays were normal. Cerebrospinal fluid was normal in content and under normal pressure.

On operation a left parietal flap was turned down and a large angioma involving the lips of the Sylvian fissure was disclosed. No attempt at removal was made.

Auditory function: Tympanic membranes normal. Hearing: Whisper, right and left greater than 20 ft.

Case 10.—G. S., male, aged 49, admitted under the care of Dr. E. A. Carmichael on January 24, 1941. Six years previously while sitting in a chair his face became distorted and his "right arm and leg became useless." He could not speak: About one month later function began to return in his arm and leg, but his speech showed no improvement for six to eight months, after which it slowly improved. Four to six months after the onset of the weakness he had a generalized epileptiform attack with loss of consciousness. There were three such attacks, the last being four years ago. After each fit his speech became worse and his right limbs weaker. Following these he did not regain his previous strength for three months.

Past history: Rheumatic fever when aged 23, following which he was diagnosed as having valvular disease of the heart.

On examination: A healthy co-operative patient. He had little difficulty of comprehension of speech and could carry out complicated requests correctly. He had much difficulty in finding spoken and written words to express what he wanted to say. He had difficulty also in naming objects, though he could identify objects named in speech or writing.

Cranial nerves: Apart from right lower facial weakness and defective closure of the right eye nothing abnormal could be detected.

Motor and sensory system: Within normal limits right and left, apart from a right extensor plantar response, and absent abdominal reflexes on the right side.

Cardiovascular system: Mitral diastolic murmur and thrill, fibrillating, pulse 70 per minute. Blood pressure, 120/80.

A diagnosis of left middle cerebral embolism was made; residual damage involving Broca's area on the left side.

Auditory function: Tympanic membranes normal. Hearing: Whisper, greater than 20 ft. right and left.

Our thanks are due to the staff of the National Hospital for their kindness in allowing us to examine the patients under their care and to Dr. E. Arnold Carmichael, Director of Research, for his helpful criticism. Where not otherwise stated all operations referred to in the Appendix were performed by Mr. Harvey Jackson at the Neuro-surgical Unit, Hurstwood Park E.M.S. Hospital. We wish also to thank Mr. W. McKissock for the facilities so willingly provided for the examination of patients under his care at the Neuro-surgical Unit, Leavesden E.M.S. Hospital. The work was carried out on behalf of the Medical Research Council.

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STUDIES IN HUMAN VESTIBULAR FUNCTION: II. OBSERVATIONS ON THE DIRECTIONAL PREPONDERANCE OF CALORIC NYSTAGMUS ("NYSTAGMUSBEREITSCHAFT") RESULTING FROM UNILATERAL LABYRINTHECTOMY.

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Introduction.

Since the work of Cornelius Winkler (1907) few matters have received such searching attention at the hands of vestibular physiologists as the effects of unilateral ablation of the mammalian labyrinth. It is well established that these effects arise from paralytic processes in the affected labyrinth since they are precisely matched by its cocainization; while their further attribution to unbalanced tonic impulses proceeding from the opposite labyrinth has been proven by their cancellation following a secondary ablation of that organ.

As summarized by Magnus (1924), the following are the chief results observed:—

(1) Nystagmus to the opposite side.

(2) Rotation of the head and neck in a direction which brings the *normal* labyrinth uppermost.

(3) Secondary rotation of the spine and increased extensor tone of the opposite limbs ("Grunddrehung").

Comparable studies in the case of man have of necessity been much more sporadic and incomplete. Nevertheless, the results as established by Bárány and others show that they differ widely from those obtained in animals. As in animals, nystagmus to the opposite side is a marked feature. "Grunddrehung," however, is absent, while the direction of rotation of the head and neck is such as to bring the *affected* labyrinth uppermost. It must of course be emphasized that the conditions of labyrinth destruction in many of these individuals forbids any ready com-

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parison of the results with those obtained by the acute destruction of a normal organ as in the case of Magnus's animals. In man, the destroyed labyrinth is frequently the seat of previous disease, often of long standing and of uncertain severity, and apparent "anomalies" in the results of its destruction can with some reason be attributed in part to these facts. That the matter can be explained wholly or even substantially in this way is, however, by no means certain. In spite of the wide variations in the biological conditions under which labyrinth destruction is achieved by disease or surgery, its results appear to be remarkably constant. In addition, the absence of any precise anatomical evidence upon the orientation of the macula of the human utricle leaves open the possibility that the peculiar character of the clinical results of labyrinth destruction in man may be capable of an anatomical explanation.

For these reasons it would seem particularly desirable to avoid basing any study of the results of labyrinth destruction in the human subject upon those so well established by animal experiment. In the present work it has accordingly been our primary aim to consider these human findings more fully and upon their own merits, and with particular reference to the occurrence and course of directional preponderance of induced vestibular nystagmus. This has been studied chiefly by caloric stimulation of the unaffected labyrinth by means of the technique already described in the preceding paper.

Methods.

The caloric tests have been used according to the technique described in the preceding paper. It is clear that the demonstration of directional preponderance of caloric nystagmus following unilateral labyrinthectomy must be left dependent upon a disturbance of the normal relationship of the cold and hot reactions of the opposite ear. As was pointed out in discussing the rationale of this technique (p. 122), such a demonstration should be quite feasible, and this has been fully verified by our experiences in the present investigations.

Material.

This consisted of nine subjects in whom unilateral destruction of the labyrinth by surgical measures had been carried out on account of intractable vertigo due to Ménière's disease.

Recent histological work (Hallpike and Cairns, 1938; Hallpike and Wright, 1939; Rollin, 1940) has now fully demonstrated that the disease process responsible for this disorder is located within the labyrinth, and

that the morphological changes consist essentially of a dilatation of the endolymphatic system with a concurrent increase of fluid pressure which leads in turn to paresis of the nervous mechanism of the labyrinth. The pathological anatomy of the labyrinthine changes will be more fully discussed in the succeeding paper, but what has been said will suffice to establish the elementary standpoint that a labyrinth destroyed for the relief of Ménière's disease must be looked upon as being already the seat of a disease process causing paresis varying in degree and distribution of its contained sense organs.

All the present nine subjects were clinically typical of Ménière's disease in exhibiting paroxysmal vertigo with vomiting and nausea of varying severity, accompanied by tinnitus and deafness in the absence of other neurological abnormalities. Caloric tests carried out before operation showed significant changes in all. In seven the change found was of the canal paresis type in the deafer ear. In the remaining two cases directional preponderance was found towards the better hearing ear. Following the operation all took up the characteristic position in bed with the affected ear uppermost and showed marked spontaneous nystagmus to the opposite side. These phenomena subsided in all cases within a week, and further caloric tests were carried out, in some cases as soon as the nystagmus had ceased and the patient was able to lie with comfort on his back.

Results.

Following the operation complete deafness of the affected ear with absence of a response even to strong caloric stimulation was observed in all cases. The caloric reactions of the opposite ear were then repeated in accordance with the standardized technique. In all cases there was revealed a striking and well systematized variety of change in the normal relationship of the two reactions, consisting of an increase of the hot and a concurrent diminution of the cold responses with respect to one another, and so constituting a marked directional preponderance of caloric nystagmus to the side of the intact ear. The mean level of the two responses was not materially affected. Further caloric tests were carried out at intervals up to seventeen months, and it was shown that this alteration in the normal relationship of the hot and cold reactions of the intact ear underwent a considerable degree of restoration to normal in the course of time.

The clinical features and particulars of the caloric findings in two characteristic cases of this series will now be described in detail.

(1) G. A., male, aged 38. Eighteen months' history of vertigo with occasional vomiting and increasing deafness of the right ear. Slight retraction of both tympanic membranes. Internal ear deafness of right ear with high tone loss. The right labyrinth was destroyed on September 17, 1941.

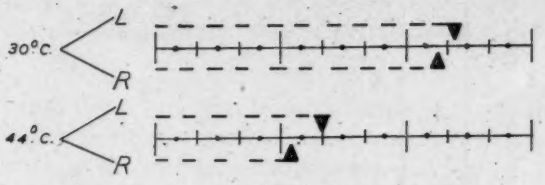


FIG. 1 (*Case 1*).—Reactions before operation.

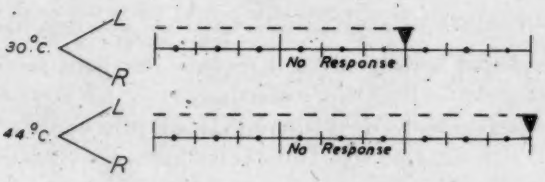


FIG. 2 (*Case 1*).—Reactions three weeks after right labyrinthectomy.

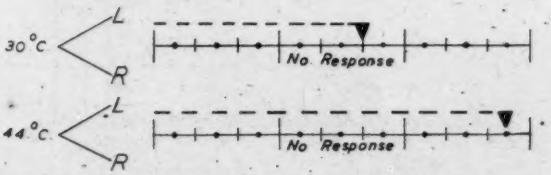


FIG. 3 (*Case 1*).—Reactions 30 weeks after right labyrinthectomy.

Before operation caloric tests revealed a slight right canal paresis as represented in fig. 1. Reactions 1 and 3 of the left canal show a normal relationship. A repetition of the tests upon the intact ear three weeks after the operation revealed a marked disturbance of this relationship, which is shown in fig. 2; reaction 1 being reduced to two minutes, and reaction 3 increased to three minutes. Further tests were carried out later, and eight weeks after the operation the exaggeration of the hot reaction was somewhat reduced. Fig. 3 shows the result of the final test carried out thirty weeks after the destruction of the right labyrinth. The

full course of the caloric reactions of the left ear and of their disturbed relationship is shown diagrammatically in fig. 4. Time in days from the first test is plotted horizontally and response durations vertically. The continuous and dotted lines refer respectively to the hot and cold responses, and the destruction of the right labyrinth is indicated by the arrow.

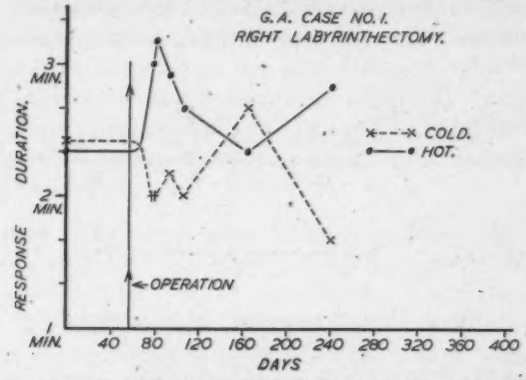


FIG. 4 (*Case 1*).—Course of caloric reactions before and after right labyrinthectomy.

(2) M. B., female, aged 46. Three years' history of paroxysmal vertigo

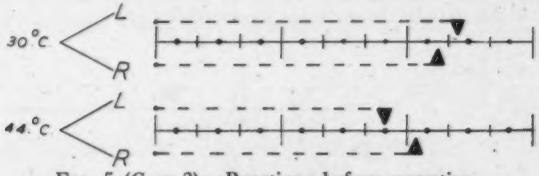


FIG. 5 (*Case 2*).—Reactions before operation.

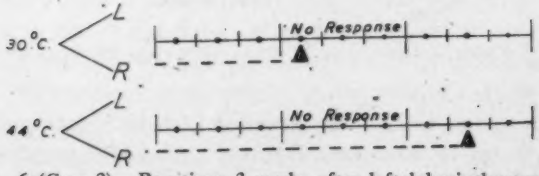


FIG. 6 (*Case 2*).—Reactions 3 weeks after left labyrinthectomy.

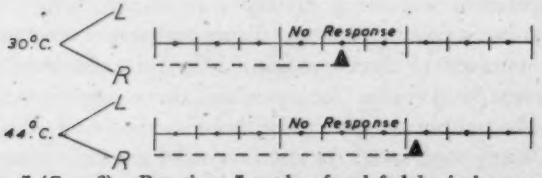


FIG. 7 (*Case 2*).—Reactions 7 weeks after left labyrinthectomy.

with vomiting and nausea preceded by deafness in the left ear and tinnitus. The tympanic membranes were normal, and there was severe deafness of the left ear of the internal ear type. The left labyrinth was destroyed on March 18, 1942. Caloric tests carried out before the operation revealed a definite directional preponderance of nystagmus to the right. This is represented in fig. 5, in which is shown the preponderance of the nystagmus-to-the-right reactions 1 and 4 over the nystagmus-to-the-left reactions 2 and 3.

A repetition of the caloric tests upon the intact right ear three weeks after the operation revealed a marked accentuation of the hot response, reaction 2 being now diminished to 1.10 minutes, and reaction 4 increased to 2.30 minutes. A further test was carried out two weeks later and showed some return to the condition of the responses prior to the operation, while fig. 7 shows the result of the final test carried out seven weeks after destruction of the left labyrinth.

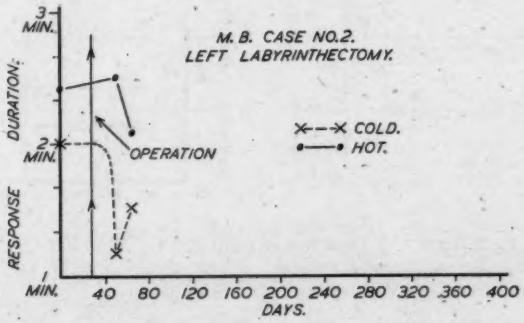
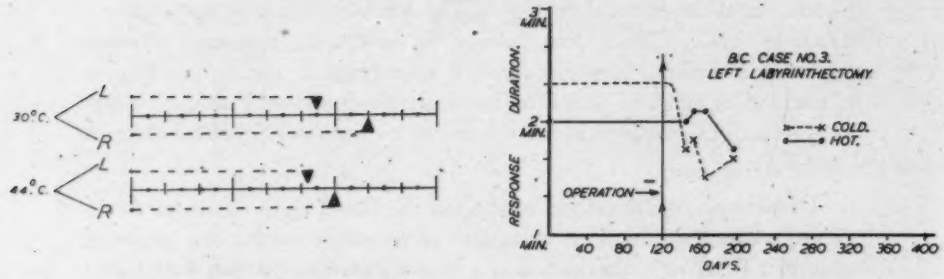


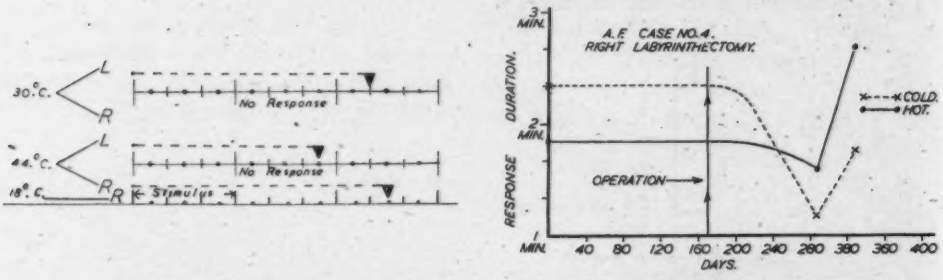
FIG. 8 (*Case* 2).—Course of caloric reactions before and after left labyrinthectomy.

The full course of the caloric reactions of the right labyrinth and of their disturbed relationship is shown graphically in fig. 8, while details of the caloric reactions of the remaining seven cases, together with summaries of the clinical particulars, are assembled in Table I. (Details of the clinical features of these nine cases are also given in the succeeding paper. Case numbers 18, 8, 25, 34, 35, 14, 15, 36, 2.) Two diagrams are given in each case. That upon the left gives the results of the first caloric tests carried out upon *both* ears before labyrinthectomy. That upon the right gives the full course of the cold and hot reactions of the unoperated ear before and after the labyrinthectomy.

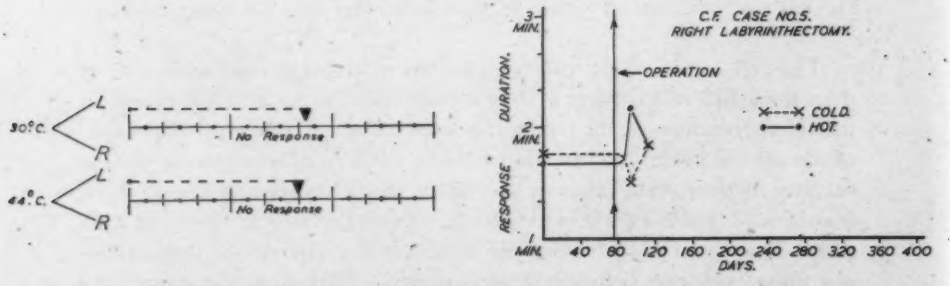
TABLE I.



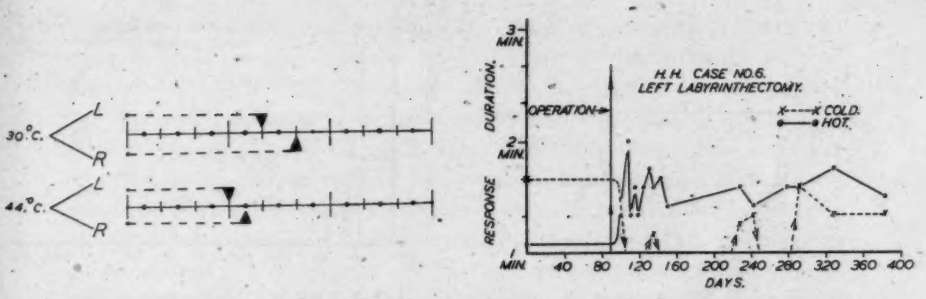
Case 3.—B. C. ♂ Aged 56. Tinnitus and deafness of left ear 5 years. Vertigo with vomiting 1 year. Tympanic membranes normal. Moderate deafness left ear. Internal ear type. Initial caloric tests: Moderate left canal paresis.



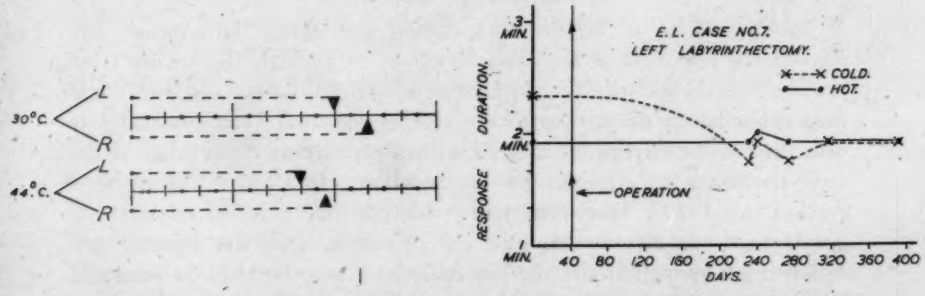
Case 4.—A. F. ♂ Aged 33. Deafness of right ear 4 years. Vertigo with vomiting 5 years. Tympanic membranes normal. Severe deafness right ear. Internal ear type. Initial caloric tests: Very severe right canal paresis.



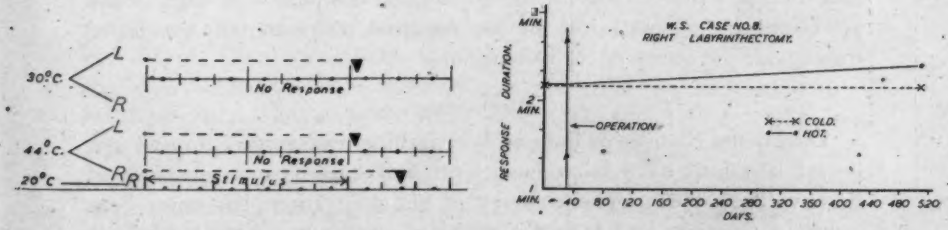
Case 5.—C. F. ♂ Aged 47. Tinnitus and deafness of right ear 10 years. Vertigo with vomiting 4 years. Tympanic membranes normal. Severe deafness right ear. Internal ear type. Initial caloric tests: Very severe right canal paresis.



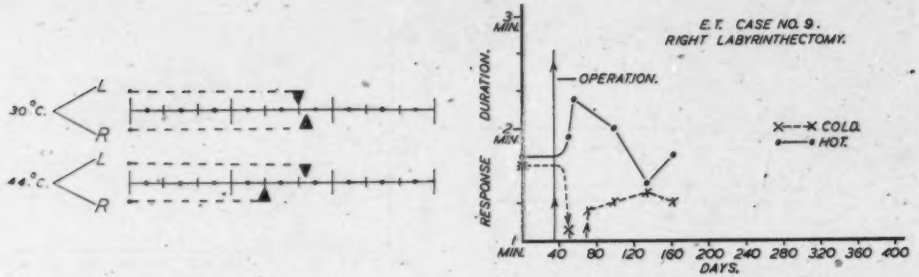
Case 6.—H. H. ♂ Aged 42. Tinnitus left ear 5 years. Deafness left ear 10 years. Vertigo with nausea and vomiting 6 months. Tympanic membranes scarred. Severe deafness left ear. Internal ear type. Initial caloric tests: Moderate left canal paresis.



Case 7.—E. L. ♀ Aged 45. Tinnitus left ear 5 years. Deafness left ear 11 weeks. Vertigo with nausea and vomiting 11 weeks. Left tympanic membrane retracted and opaque. Severe deafness left ear. Internal ear type. Initial caloric tests: Moderate left canal paresis.



Case 8.—W. S. ♂ Aged 53. Tinnitus right ear 12 years. Deafness right ear 2 years. Vertigo 2 years. Tympanic membranes normal. Complete deafness right ear. Moderate deafness left ear. Internal ear type. Initial caloric tests: Very severe right canal paresis.



Case 9.—E. T. ♀ Aged 32. Tinnitus in right ear 3 years. Vertigo with nausea 3 years. Tympanic membranes normal. Slight deafness both ears. Right greater than left. Internal ear type. Initial caloric tests: Directional preponderance to the left.

Summary of Results.

In Cases 1 to 8, caloric tests carried out before labyrinthectomy showed the responses of the opposite ear to be normal. Following labyrinthectomy these tests all showed the development of a marked directional preponderance of nystagmus to the side of the intact ear, consisting as described of an increase in the hot with a concurrent diminution in the cold responses with respect to one another. In Case 9, caloric tests carried out before labyrinthectomy showed that this directional preponderance was already manifest in the responses of the opposite ear. Following labyrinthectomy the preponderance was found to be increased in this case. Further observations carried out over periods up to seventeen months showed a marked tendency in all nine cases towards the restoration of the normal relationship of the cold and hot responses of the intact ear. This process of restoration was at first rapid. Later it became much slower, and in no case became complete. In each of the nine cases the mean level of the two responses was materially unaffected throughout the course of the observations.

Discussion.

Directional changes of induced labyrinthine nystagmus following unilateral labyrinth destruction have been well known since the time of Bárány (1906, 1907). The accuracy of his observations has never been called in question, and indeed they have ever since constituted a well-established land-mark of our knowledge in this field.

Nearly all Bárány's work on the effects of labyrinth destruction was based upon the study of patients suffering from labyrinthitis resulting

usually from suppurative otitis media. With few exceptions these first came under investigation in the stage of acute labyrinth destruction and then presented the typical syndrome of complete deafness of the affected ear, spontaneous nystagmus to the opposite ear and a characteristic posture in bed with the affected ear uppermost. Following the subsidence of the spontaneous nystagmus, Bárány then carried out certain observations upon post-rotational nystagmus and was able to establish the constant occurrence of well-defined abnormalities in these reactions, which he described as characteristic of latent destruction of one labyrinth. Bárány had already standardized and put upon a quantitative basis the technique of rotational stimulation of the external canals, and had established by these means that the duration of post-rotatory nystagmus in the normal individual was approximately equal in both directions. Following unilateral labyrinth destruction by suppuration this was constantly found to be replaced by a striking preponderance of post-rotatory nystagmus to the sound ear, amounting in the case of a left labyrinth destruction to an accentuation of nystagmus to the right following the cessation of rotation to the left.

These findings were explained by Bárány upon the basis of Ewald's law. It will be recalled that according to Ewald (1892) the sensitivity of the external canal cupula to endolymph movement is largely uni-directional, the response being large when the flow is ampullo-petal and small when the flow is ampullo-fugal. According to this view the nystagmic responses which follow the cessation of rotation to the left and right are regarded as arising principally from the right and left canals respectively, and are normally of equal duration. Bárány seems to have expected that upon this basis the elimination of one canal by labyrinth destruction would merely leave the opposite canal and its associated neural elements working as before, and so result in a preponderance in the nystagmic response (to the sound ear) of a rotational stimulus causing an ampullo-petal flow of the endolymph. In the event this was found to be in exact agreement with the observed facts, and his findings of a preponderance of post-rotatory nystagmus to the sound ear following unilateral labyrinth destruction were accordingly explained on the apparently satisfactory basis of Ewald's law. Bárány repeated his examinations and recognized that this preponderance of post-rotational nystagmus to the sound side tended to disappear in the course of time, and he attributed this to compensatory processes within the central nervous system. A consideration of the caloric test diagrams in figs. 4 and 8 and in Table I shows that in all of our cases there occurred following the operative destruction of the labyrinth a striking accentuation

of the nystagmic response towards the sound ear evoked by hot stimulation of the external canal, and that as in Bárány's cases, this accentuation showed a marked diminution with time.

If the attention be confined to the caloric responses *following* labyrinth destruction the resemblance of our findings within this time period to those of Bárány is striking, and leaves little room for doubt that the phenomena under observation had an identical basis. In respect therefore of so much of the observational facts, our own and Bárány's findings are in full agreement. Regarding their interpretation, however, the additional data now at our disposal make it difficult to regard Bárány's explanation as the correct one. In the first place it would seem clear that our own quantitative estimations of the normal caloric responses in man are quite incompatible with the view that Ewald's law can validly be applied to the intact human subject. As postulated by Bárány, and since fully confirmed, hot stimulation of the external canal wall engenders an ampullo-petal flow of endolymph. In the case of a cold stimulus the direction of this flow would be reversed. In these circumstances Ewald's law clearly demands that the physiological effect of the hot stimulus should greatly exceed that of a thermally equivalent cold stimulus. Our own investigations of the quantitative aspects of the caloric reaction of normal subjects have been fully described in the preceding paper to which reference may be made. As standardized, the technique provides cold and hot stimuli which are thermally equivalent with respect to body temperature (cold, 30° C.; hot, 44° C.), and Ewald's law would certainly lead us to expect that the latter stimulus would be the more effective of the two. In 10 per cent. only of our normal subjects has this proved to be the case, while the great majority showed a marked accentuation of the response to cold. These findings are thus in so strong disagreement with Ewald's law as in our view to make impossible its application to the intact human subject. The present investigation has also provided information beyond that available to Bárány, in that it has been possible in our cases to investigate the caloric reactions of the sound ear *before* the destruction of the labyrinth.

This has proved to be of particular significance in eight of our nine cases in which these reactions before operation were found to be normal, more especially in respect of the relative durations of the hot and cold responses. A further reference to the test results of Cases 1 and 2 and to Cases 3 to 8 in Table I now makes it clear that the effect of destruction of the opposite labyrinth has been in all cases to alter the previously normal bi-directional sensitivity to endolymph flow of the external canal to the

uni-directional type of sensitivity recognized by Bárány, and that its original bi-directional sensitivity tends to be re-established in the course of time. The canal itself has remained intact throughout and it is consequently necessary to attribute all of the observed alterations in its reactions to changes in the neural mechanism of its central connections. It can now be seen that wide differences exist between our own and Bárány's interpretation of the changes in the responses of the external canal which follow extirpation of the opposite labyrinth, and that these differences involve certain basic principles which have long been regarded as well founded. For the purpose of comparison the two views will accordingly be re-stated in summarized form.

(1) Bárány followed Ewald in regarding the normal sensitivity to endolymph movement of the external canal cupula as being predominantly uni-directional, the response being evoked chiefly by an ampullo-petal flow of the endolymph. The nystagmic reactions which follow the cessation of rotation to the left and right were consequently to be regarded as being initiated by the right and left canals respectively, and being normally of equal duration. Bárány considered that removal of one canal by destruction of the labyrinth would lead by a simple process of subtraction to a situation in which the opposite canal and its nervous connections would be left alone to react in accordance with its normal uni-directional sensitivity, and that in the course of time this normal type of sensitivity would be converted into an abnormal bi-directional type by central compensatory processes.

(2) Our own views are that the quantitative data on the caloric reactions of normal human subjects which are given in the preceding paper (and were not available to Bárány) establish clearly that in contradiction to Ewald's law the normal sensitivity of the human external canal is bi-directional being equally evoked by endolymph flow in either direction. Following destruction of the opposite labyrinth this normal type of sensitivity is converted into an abnormal uni-directional type. Later, the normal bi-directional sensitivity tends to be restored. Both these variations in the normal responses of the canal which follow destruction of the opposite labyrinth are due to changes in the central nervous mechanism.

Some further discussion may be directed to the possible nature of the central processes which must be deemed responsible for the upset of the normal caloric responses effected by destruction of the opposite labyrinth and for its later partial restoration.

Two aspects of these findings call for particular consideration. Firstly,

the nature of the underlying changes in the central vestibular mechanism to which the findings are attributed; and secondly, their relationship to the directional preponderance of caloric nystagmus due to cerebral lesions which is the subject of the preceding paper.

The Central Mechanism Responsible for the Appearance of Directional Preponderance of Caloric Nystagmus Following Unilateral Labyrinthectomy.

The most rational line of approach to this question is suggested by the correspondence in direction and unbroken transition between the spontaneous nystagmus which immediately follows unilateral labyrinthine destruction and the directional preponderance of caloric nystagmus which is observed later; for if for these reasons we adopt the obvious view that the latter is a residuum of the former then both become explicable upon a common basis.

An explanation of the mechanism of spontaneous nystagmus which follows unilateral destruction of the labyrinth is best provided upon the basis of current and well-founded views on the normal control of ocular posture by tonic impulses from the labyrinths. According to these views there is held to exist a state of balance between the vestibular nuclei on each side of the brain stem which feed the ocular muscles by way of their motor nuclei. Each of these nuclei (or groups of nuclei) is fed by tonic impulses from the homolateral labyrinth, the two groups of impulses being in mutual opposition with respect to their effect upon ocular posture. (It is of interest to note how little, if at all, this general statement of principle is found to differ from the penetrating conclusions reached by Högyes so long ago as 1881, and particular attention is drawn to the relevant portions of Súgars German translation of Högyes papers published in 1913 (p. 134).)

Destruction of one labyrinth, of its associated vestibular nuclei, or of the intervening nervous connections, leads to a preponderance of the tonic impulses to the eye muscles leaving the opposite vestibular nuclei and results in nystagmus or ocular deviations of which the nature and extent are dependent upon the species of animal, the presence of narcosis and other factors. In the conscious human subject the effect of unilateral labyrinth destruction is of course nystagmus to the opposite side, which, as we now see the matter, gives place in time to a preponderance over the cold of the hot caloric response of the opposite external canal, and there seems little reason at this stage for not accepting the view that this

directional preponderance is due to the persistence in a diminishing form of the preponderance of tonic impulses reaching the ocular muscles from the opposite labyrinth by way of its vestibular nuclei.

The Central Mechanism Responsible for the Diminution of Directional Preponderance of Caloric Nystagmus Following Unilateral Labyrinthectomy.

Turning now to an explanation of the compensatory neural mechanism which leads to disappearance of the spontaneous nystagmus and to the gradual diminution of the subsequent directional preponderance an obvious line of approach is again suggested by what is known of the closely allied and better studied processes which are responsible for the so-called compensatory nystagmus of Bechterew. Bechterew (1883) showed that if a suitable interval be allowed to elapse after the abatement of the nystagmus and rolling movements which follow unilateral labyrinth destruction in animals, the subsequent destruction of the second labyrinth would then lead to further nystagmus and rolling movements as if the first labyrinth were intact. No nystagmus or rolling movements occur if both labyrinths are extirpated together, and the condition which then results is characterized by great weakness of the limbs with the animal lying flat upon its belly and beating upon the ground with its chin. Further experimental work which bears upon the subject of Bechterew's nystagmus has been ably reviewed by Spiegel (1938), and the summarized account which follows of its more important facts and conclusions are mainly derived from this source.

It is generally agreed that the effects of labyrinthectomy are paralytic in nature and due to the elimination of tonic impulses passing from the labyrinth to the vestibular nuclei of the same side. The elimination of these impulses is compensated by an increase in the activity of these nuclei, a statement which is based upon the finding that following the abatement of the symptoms due to destruction of the labyrinth, these symptoms may be renewed in the same form by destruction of the nuclei. It follows that if the process of compensation for the destruction of the first labyrinth (say the left) is due as stated to enhanced activity of its associated vestibular nuclei, then Bechterew's nystagmus which follows destruction of the second (right) labyrinth must be due to a temporary preponderance of the already compensated activity of the left vestibular nuclei, which in turn becomes similarly compensated by an increased spontaneous activity of the right vestibular nuclei. This is confirmed by the finding that destruction

of the left nuclei at the same time as destruction of the right labyrinth prevents the occurrence of Bechterew's nystagmus. Finally, following the abatement of symptoms after destruction of the second labyrinth, the further destruction of left or right vestibular nuclei gives results which are essentially the same as those which follow destruction of the left or right labyrinths of the intact animal. The compensatory increase in activity of the vestibular nuclei on one side following destruction of the homolateral labyrinth may be spontaneous or due alternatively to the enhancement of impulses reaching it from the cerebellum, cerebrum or elsewhere. The former explanation is favoured by the finding that Bechterew's nystagmus is not prevented by decerebration or by removal of the cerebellum, and is likewise uninfluenced by ocular impressions or by posterior cervical rhizotomy. These facts convey a clear suggestion that within the nerve complex of the vestibular nuclei there is contained some mechanism which is capable of re-establishing a balance in the outflow from the two sets of nuclei of tonic impulses to the eye muscles and elsewhere in the face of unbalanced inflow due to the paresis of one or other labyrinth. The process of compensation consists, in effect, of an increase in the spontaneous activity of the particular set of nuclei from which the tonic labyrinthine impulses are cut off.

This then is the neural mechanism which is responsible for eliminating the major disturbances of posture which follow unilateral labyrinthectomy; and since we regard directional proponderance of caloric nystagmus as a residuum of these major disturbances it follows that its diminution with time can also be regarded as dependent upon the same mechanism.

It is now possible upon the basis of this information to reconstruct in diagrammatic form the vestibulo-oculo neural network with its labyrinthine and cortical subdivisions which control the normal posture of the eyes in the horizontal plane. It is stressed that the diagram (fig. 9) deals only with the tonic impulses reaching the vestibular nuclei from the labyrinths and, as now also seems likely, from the temporal lobes. Their integration with the phasic impulses which reach these nuclei from the canal organs in response to thermal or rotational stimulation will be considered later. In order to facilitate their rendering in a schema of this sort it has been found desirable to reduce to their simplest terms the various anatomical and physiological components for which a place has to be found. Thus the two eyes with four muscles will be replaced by a single eye with two muscles only, which turn it to left and right. For similar reasons it is convenient to ignore the quick component of nystagmus. Vestibular

nystagmus itself is a compound ocular movement of which the slow component is the primary element. It is always derived from a preponderance of impulses leaving one or other of the vestibular nuclei, and in the present

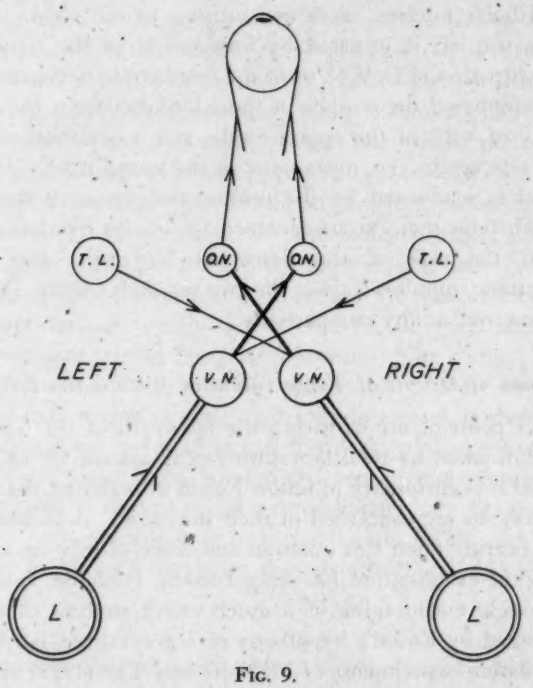


FIG. 9.

instance we are limited to the case of a preponderance due to elimination of tonic impulses arising in one or other labyrinth. The quick movement is initiated by the slow through a reflex mechanism subserved by certain subsidiary cell groups which are closely attached to the vestibular nuclei, and believed by de Nó (1933) to be located within the substantia reticularis. It is true that the direction of nystagmus is determined as a matter of custom by the direction of its quick component. For the present purpose, however, it is necessary to consider only the true labyrinthine or slow component, and the quick or secondary component will accordingly be ignored. The building up of the schema is best approached from its labyrinthine aspect which is contained in the lower part of fig. 9 and will be dealt with first.

Tonic impulses pass from the left and right labyrinths (L.) to the homo-

lateral vestibular nuclei (V.N.). From each of these the outflow passes to the motor nucleus on the opposite side of the brain-stem which subserve a turning movement of the eye to the opposite side. Thus impulses from the left vestibular nucleus cause eye turning to the right. Conversely, a turning to the left is initiated by impulses from the right vestibular nucleus. Extirpation of L, V.N. or of the intervening nerve tract on either side leaves unopposed the outflow of tonic impulses from the intact labyrinth by way of V.N. of the opposite side, and a deviation of the eye to the injured side results (i.e. nystagmus to the sound side). As described, this situation is readjusted by the central compensatory mechanism of Bechterew whereby there occurs an increase in the spontaneous activity of V.N. on the side of the destroyed labyrinth; and a balance between the tonic impulses leaving the two vestibular nuclei (V.N.) is thus eventually restored, at any rate partially.

The Point of Origin of Tonic Impulses Within the Labyrinth.

The exact point of origin within the labyrinth of the tonic impulses which are eliminated by total labyrinthectomy cannot yet be stated with certainty, and it is customary to follow Ewald in believing that both canal and otolith organs are concerned in their initiation. A considerable bulk of evidence bearing upon this question and based chiefly upon the results of physiological examination has since become available, and its general trend is strongly encouraging of a much closer analysis of the position that is connoted by Ewald's hypothesis of a generalized labyrinth tonus. Thus the ablation experiments of McNally and Tait (1925) upon the frog and rattlesnake, and of Versteegh (1927) upon the rabbit have considerably narrowed the field by excluding the equilibrial function of the saccule, a result which has been corroborated by the electro-physiological work of Ashcroft and Hallpike in 1934 which provided positive evidence of the function of this organ as a vibration receptor.

The existence of tonic impulses from the canal organs cannot be so fully excluded. Thus Löwenstein and Sand (1936) were able to show the existence of a steady stream of impulses from the resting canal organs of the dog-fish, while Huizinga (1932) described changes in neck muscle tonus of the pigeon following isolated lesions of its canal system which he attributed to the elimination of tonic impulses arising therein. On the other hand no definite postural changes were ever observed by McNally and Tait (1925) in their ablation experiments upon the canal nerves of the frog which are certainly the best of their kind which have been

recorded. Similarly, Ross (1936) who investigated the electrical activity of the 8th nerve in the frog was able to record brisk phasic responses to rotation from certain regions of the nerve which remained irresponsive in the resting state of the preparation. Thus the experimental evidence of tonic impulses from the canal organs would appear to vary in different animal forms and none has so far been obtained of their occurrence in man.

Considering finally the remaining organ within the labyrinth which might be a source of tonic impulses, namely the utricle, the most decisive evidence at our disposal is again provided by McNally and Tait (1925) who observed no postural disturbance in the frog following any lesion or combination of lesions which left the utricles intact, although such effects were striking and persistent following utricular damage of any kind. For these reasons it seems justifiable to regard the human utricle as much the most important, if not the sole source, of the tonic impulses which reach the vestibular centres from the labyrinth. The clinical implications of this conclusion seem likely to be considerable. As we have seen, it is the unilateral elimination of these tonic impulses which leads to the phenomenon of directional preponderance of caloric nystagmus. If then, as appears probable, they arise wholly or even preponderantly from the utricle, it follows that directional preponderance can be regarded as a physical sign pathognomonic of utricular paresis. This and other possibilities of the differential diagnosis of labyrinthine lesions will be further discussed.

The Differential Diagnosis of Labyrinthine Lesions by Means of the Caloric Tests.

A. Utricular paresis.—Fig. 9 shows the pathway of tonic impulses from the labyrinths (i.e. utricles) to the vestibular nuclei. As explained, elimination of one utricle leads to nystagmus to the opposite side due to unbalanced action of the impulses leaving the nuclei from the opposite utricle. This condition becomes partially compensated by Bechterew's mechanism and a residual state results in which is observed the phenomenon of directional preponderance of caloric nystagmus also to the opposite side. The integration with this scheme of nystagmus provoking impulses from the external canals is conveniently achieved by regarding those impulses as essentially phasic, as arising, that is to say, only in response to and during cupular movements brought about by rotational or thermal stimuli. Thus in a normal individual they produce nystagmus by a transient reinforcement of the outflow from one or other vestibular nucleus. In the

presence of a directional preponderance due to a utricular paresis the initiation of impulses from the external canal organs of either ear remains unchanged. Nevertheless, their effect in producing nystagmus is strikingly modified by the selective augmentation of all such impulses which evoke nystagmus in the direction of the intact utricle. This seems to provide a serviceable explanation of the physiological basis of directional preponderance of caloric nystagmus due to a labyrinthine lesion. Its occurrence is regarded as evidence of paresis of the opposite utricle with normal function of both external canals.

B. Canal paresis.—Loss of function of the external canal organ leads only to a diminution of the phasic impulses which are initiated therefrom by cupular movements brought about by rotational or thermal stimuli. Its nystagmic responses to cold and hot stimulation are equally reduced, while no alteration occurs in the relationship of the cold and hot reactions of the opposite ear, so establishing the absence of directional preponderance (i.e. due to a utricular paresis). These considerations provide a rationale for regarding this type of abnormality of the caloric reactions as diagnostic of external canal paresis with normal utricles, and reference should be made to figs. 4 and 5 of the preceding paper which show caloric test diagrams which are typical respectively of *paresis* of the left and right external canals.

C. Utricular paresis and canal paresis in combination.—It will be seen from what goes before that we believe it possible by means of the caloric reactions to effect a differential diagnosis between *paretic* lesions of the utricle and external canal. Since such lesions must on occasions occur in combination it follows that this might be revealed by the occurrence of an appropriate combination of their individual caloric reaction patterns. A variety of such combinations at once suggest themselves. For example, left canal + left utricle. Right canal + right utricle, &c. In theory, each of these combinations might arise in the natural course of chronic labyrinthine disease, and in theory also, each might be recognizable by its particular pattern of caloric reaction; a pattern to which the key might be derived from its two primary elements already defined as characteristic of utricular and canal paresis. The subject is pursued in some detail in the succeeding paper in which these principles will be systemically applied to the interpretation of anomalies in the caloric reactions observed in a number of subjects suffering from a variety of partial labyrinthine lesions which are found in the course of Ménière's disease.

The Functional Relationship of the Utricles and the Temporal Lobes in Determining the Occurrence of Directional Preponderance of Caloric Nystagmus.

It remains to consider the relationship of the directional preponderance of caloric nystagmus due to unilateral elimination of tonic labyrinthine impulses to the similar type of disturbance which has now been observed in association with lesions of the temporal lobe, and which forms the subject of the preceding paper. In both instances the disturbances arise from disease or destruction of what may be described as outlying subsidiaries of the central vestibulo-oculo network. The tonic impulses from the labyrinthine subsidiaries, in all probability the utricles, are shown in fig. 9 to converge upon the vestibular nuclei and are thence relayed to the motor nuclei of the ocular muscles. As has also been explained, the vestibular nuclei comprise some mechanism which is capable of restoring to balance their outflow of tonic impulses in the face of unbalanced inflow from the utricles, and the operation of this mechanism is seen in an extreme case in the phenomena associated with Bechterew's nystagmus. Although much less can be said of the cortical subsidiaries it would seem well within the bounds of possibility that the same anatomical and physiological pattern is preserved by a similar convergence upon the vestibular nuclei of tonic impulses from the temporal lobes. Certainly such a view would appear to be a serviceable one if only as a basis for further investigation, and it has accordingly been incorporated in the upper portion of fig. 9. According to this, tonic impulses from the temporal lobes are shown proceeding to the opposite vestibular nuclei and so leading to ocular deviation to the side of their origin. Disease or ablation of a temporal lobe would thus lead to preponderance of the tonic impulses from the opposite lobe, with a tendency to ocular deviation in that direction, amounting, that is to say, to a directional preponderance of caloric nystagmus to the side of the lesion, so according with the observations recorded in the preceding paper.

In putting forward this hypothesis two gaps in our knowledge demand particular emphasis. Nothing is known of the functional modality of the impulses which reach the vestibular nuclei from the temporal lobes. They are represented in fig. 9 as reinforcing the labyrinthine impulses which leave the opposite vestibular nuclei, but the same functional result would obviously be achieved if they exerted an inhibitory effect on the labyrinthine impulses leaving the vestibular nuclei on the same side. The question is clearly one which awaits further information.

We are almost as much in the dark regarding the occurrence of compensatory processes following destruction of the temporal lobe akin to those which underlie Bechterew's nystagmus. Assuming that such processes occur certain observations make it evident that whatever their nature they may remain incomplete after a period of years. We refer in particular to Cases 3 and 9 of Group II in the appendix to the preceding paper in which the clinical evidence makes it likely that the temporal lobe lesions were of very long standing (two and a half years in Case 3, and ten years in Case 9).

In placing the point of convergence of cortical and labyrinthine impulses at the vestibular nuclei we are on firmer ground. The fibres conveying the labyrinthine impulses to the various ocular muscles which control nystagmus are finally distributed from these nuclei, and the impact of other impulses which play a part in the control of labyrinthine nystagmus is therefore likely to occur at this point.

One statement can be made with confidence. Compared with that of the labyrinthine impulses the rôle of the cortico-fugal impulses from the temporal lobes in controlling directional preponderance of caloric nystagmus is relatively inconspicuous. In most of our cases of directional preponderance due to temporal lobe lesions the amount of this preponderance was small (see Table II of the preceding paper), while complete suppression of a reaction opposed in direction to that of the preponderance has never been observed. In this respect a comparison should be made, with the caloric test diagrams of Cases 6 and 9 which are shown in Table I of the present paper. In both of these the reaction to cold of the opposite ear following unilateral labyrinthectomy was temporarily suppressed. The subsidiary character of the impulses which reach the vestibular nuclei from the temporal lobes has accordingly been denoted in fig. 9 by the use of fine lines to depict the course of these pathways.

Summary.

(1) A description is given of the results of the caloric tests carried out in nine patients before and after destruction of one labyrinth for intractable vertigo due to Ménière's disease.

(2) Following the subsidence of post-operative nystagmus the responses of the unoperated ear revealed in all nine cases a marked directional preponderance of caloric nystagmus to that side, diminishing with time.

(3) The phenomenon of post-operative diminution of this directional nystagmus is considered to be identical with the gradual equalization of the nystagmus responses to rotation observed by Bárány after the destruction of one labyrinth by suppuration.

(4) It is pointed out that Bárány's explanation was based upon the assumption that Ewald's law, which postulates the uni-directional sensitivity of the canal cupula to endolymph flow, could validly be applied to the intact human subject.

(5) Systematic application of the caloric tests, modified as described, to normal human subjects has now shown a bi-directional sensitivity to endolymph flow to be characteristic of the canal cupula of the intact human subject. Bárány's explanation is thereby rendered unacceptable.

(6) A new explanation is offered of the causation by unilateral labyrinthectomy of directional preponderance of induced vestibular nystagmus to the opposite side.

(7) According to this explanation the normal sensitivity to endolymph flow of the human external canal is held to be bi-directional. Its conversion into an abnormal uni-directional sensitivity by unilateral labyrinthectomy is attributed to the elimination of tonic impulses, chiefly of utricular origin.

The later restoration of the normal bi-directional sensitivity is explained upon the basis of the central compensation of Bechterew.

(8) Apart from directional preponderance attributed to unilateral paresis of the utricle, another type of disturbance in the normal reaction pattern of the caloric tests is described as characteristic of paresis of the canal organ, and the bearing of these two types of abnormality of the caloric reactions upon the differential diagnosis of labyrinthine lesions is discussed.

(9) Further consideration is devoted to the integration within the vestibular nuclei of the various tonic impulses which are concerned in the mechanism of directional preponderance of induced vestibular nystagmus. These comprise: (*a*) Vestibular impulses. In all probability these are derived chiefly from the utricles. (*b*) Cortical impulses. These are derived from the temporal lobes as suggested by the findings described in the preceding paper.

Our thanks are due to the staff of the National Hospital for their kindness in allowing us to examine the patients under their care, and to Dr. E. Arnold Carmichael, Director of Research, for his helpful criticism.

The work was carried out on behalf of the Medical Research Council.

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STUDIES IN HUMAN VESTIBULAR FUNCTION: III. OBSERVATIONS ON THE CLINICAL FEATURES OF "MÉNIÈRE'S" DISEASE: WITH ESPECIAL REFERENCE TO THE RESULTS OF THE CALORIC TESTS.

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Introduction.

In 1861 Ménière described the case of a young woman who was taken suddenly ill with vertigo and deafness of one ear accompanied by vomiting and pyrexia. She died in the course of a few days. Post-mortem examination revealed a reddish yellow coagulum in the vestibule and the case has accordingly been since regarded as one of labyrinthine hæmorrhage of either infective or leukemic origin. As is well known, Ménière's name has since come to be attached with a certain lack of discrimination to a large variety of patients in whom vertigo occurs in association with deafness. In some of these, examination reveals a definite cause for the symptoms, in the shape of some inflammatory, neoplastic or post-traumatic process involving the labyrinth, 8th nerve or its central connections. When these have been excluded, however, there remains a fairly large group of patients who present the symptoms of paroxysmal vertigo with nausea, vomiting, deafness, and often tinnitus, in the absence of other neurological abnormalities. In these the clinical findings while indicating in a general way that the ear is the seat of the disease, have provided no adequate evidence of its precise nature. And since the condition is never a cause of death the post-mortem identification of its anatomical basis has until recently remained impracticable.

The majority of English clinicians, among whom we may include Ferrier, Gowers and Lake, have all appeared to recognize the labyrinth as the seat of the disorder while being content to leave open the problem of its precise pathology. On the other hand, Watkyn-Thomas (1932) has emphasized the existence of a very contrary trend of opinion according to which the condition is regarded as a symptom-complex which may be brought about indifferently by a diversity of pathological agents acting not only upon the labyrinth, but also upon its central connections or their

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vascular supply. This situation has been considerably clarified by the results of clinical and pathological investigations which have been published since 1938. Both Crowe and Wright (1938) have emphasized that in a large proportion of these patients the signs and symptoms of cochlear and vestibular disorder present certain obvious peculiarities in their mode of onset, in their type and degree, and in the course which they pursue, at any rate over a period of years, and agree, for these reasons, in attributing them to some specific variety of labyrinthine disorder. These conclusions were strongly supported by the results of a histological examination of the temporal bones of two such cases which were published shortly afterwards by Hallpike and Cairns (1938). In both of these the affected labyrinth was found to be the seat of an extreme dilatation of the endolymph system. In each the saccule was distended to fill the cavity of the vestibule and in each Reissner's membrane was thrown back upon the bony wall of the scala vestibuli and protruded through the helicotrema with obliteration of the perilymph spaces. In both cases unusual conditions were found in the normal absorption area of the endolymph around the saccus endolymphaticus, and in neither was there any evidence of an inflammatory process within the labyrinth. Changes of the same type though of lesser degree were found in a third case (1939) in which the duration of the symptoms had been comparatively short. In view of the peculiar character of the histological changes thus revealed, and in view also of their uniform occurrence in all three cases the conclusion was reached that they should be regarded as constituting the morphological basis of a disease process *sui generis* of the labyrinth of which the essential mechanism was an obstructive distension of the endolymph system. The morphological aspect of this problem has now been consolidated by Rollin (1940) who describes changes of identical character in the affected labyrinths of all of six patients exhibiting this clinical picture.

The present paper is primarily an analytical record of the clinical findings in fifty cases of this disorder as observed in the practice of this Hospital.

In Section I these findings are examined in the light of the pathological data now available and with especial reference also to the clinical work of Crowe and Wright. In Section II the results of the caloric tests are described in detail and their significance discussed. The character of the abnormalities revealed make possible the application thereto of the diagnostic criteria of canal and utricular lesions which have been developed in the preceding paper.

Section I.—Clinical.

Consideration has been given to the following points of the history and clinical findings in all fifty patients. The results are presented in tabular form in the Appendix, and will be discussed in the following order:

I.—Sex incidence.
II.—Age incidence.
III.—Duration of vertigo when first seen.
IV.—Occurrence of nausea, vomiting and headache in association with vertigo.
V.—Mode of onset of vertigo.
VI.—Clinical evidence of oro-nasal sepsis.
VII.—Deafness (Subjective) and tinnitus.
VIII.—Deafness (Objective); methods of testing.
IX.—Deafness (Objective) and its correlation with the results of the caloric tests. Analytical table.
X.—Character of deafness revealed by Rinné and Weber tests.
XI.—Occurrence of tympanic lesions and Eustachian obstruction.
XII.—Audiograms.
XIII.—Diagnosis, treatment and results.
XIV.—Summary and comments.

I.—*Sex incidence.*

Females, 23 cases. Males, 27 cases.

II.—*Age incidence.*

Onset of vertigo.

Under 20 years	Nil
20-30 years	6 cases
30-40 years	8 cases
40-50 years	22 cases
50-60 years	12 cases
60-70 years	2 cases

III.—*Duration of vertigo when first seen.*

Under 1 year	18 cases
Between 1 and 5 years	26 cases
Between 5 and 10 years	6 cases

IV.—*Occurrence of nausea, vomiting and headache with the vertigo.*

Nausea only	2 cases
Vomiting only	6 cases
Headache only	3 cases
Nausea and vomiting	19 cases
Nausea and headache	3 cases
Nausea, vomiting and headache ...	9 cases

Nausea, vomiting and headache were absent in only 5 out of the 50 cases, and in 3 the notes were inadequate.

V.—*Mode of onset of vertigo.*

In 30 cases no aura occurred. The onset of the vertigo was rapid in 20 of these and slow in 10.

In 17 cases a definite aura was described. The onset of the vertigo was rapid in 7 of these and slow in 10.

The character of the aura took a variety of forms which are listed below and did not depend upon the speed of onset of the vertigo.

(1) Increase of tinnitus	5 cases
(2) Increase of tinnitus and deafness	4 cases
(3) Increase of tinnitus and headache	1 case
(4) Headache only	1 case
(5) Feeling of fullness in head ...	1 case
(6) Feeling of fullness in one ear ...	1 case
(7) Numb feeling in one ear	1 case
(8) Nausea only	2 cases
(9) Feeling of weakness	1 case
(10) "Visual disturbances"	1 case

VI.—*Clinical evidence of oro-nasal sepsis.*

Inquiry was made in all cases regarding the occurrence of sore throats, nasal catarrh or discharge, and a routine clinical examination made of teeth, tonsils, nose, nasopharynx and cervical glands. In 28 cases an X-ray examination of the paranasal sinuses was included. The blood Wassermann was carried out in a few cases and was negative in all.

In the absence of toothache, caries or gingival infection which was apparent to inspection no further dental opinion was obtained as to the possibility of dental infection, and systematic dental X-rays were not undertaken. A certain proportion of the patients were in any case edentulous.

Results.

No evidence of oro-nasal sepsis; X-rays of sinuses negative ...	29 cases
No evidence of oro-nasal sepsis; no X-rays of sinuses	16 cases
Antral suppuration	3 cases
Tonsillar infection	2 cases

These findings are in opposition to the views of Wright (1938) that foci of infection in the nose and throat play an important part in the etiology of Ménière's disease.

VII.—*Deafness (Subjective) and tinnitus.*

In 48 cases one or both ears were affected by one or both of these symptoms. In 24 they made their appearance prior to, and in 23 cases

concurrent with or following the onset of the vertigo. As tabulated below the results of the caloric tests in these cases are also given. The character of the vestibular lesions is discussed more fully in Section II. The cases are considered under three headings.

A.—Symptoms unilateral. 33 cases.		
Deafness only, 8 cases	Homolateral vestibular lesion	6 cases
	Contralateral vestibular lesion	1 case
	Normal reactions	1 case
Tinnitus only, 4 cases	Homolateral vestibular lesion	4 cases
Deafness and tinnitus, 21 cases	Homolateral vestibular lesion	18 cases
	Contralateral vestibular lesion	2 cases
	Normal reactions	1 case
B.—Symptoms bilateral. 15 cases		
Deafness only, nil		
Tinnitus only, 5 cases	Unilateral vestibular lesion	5 cases
Tinnitus in both ears and deafness only in one ear, 3 cases	Vestibular lesion in ear with deafness	2 cases
	Vestibular lesion in ear without deafness	1 case
Tinnitus only in one ear and deafness only in the other, 2 cases	Vestibular lesion in ear with deafness	1 case
	Normal reactions	1 case
Tinnitus and deafness in both ears, 5 cases	Unilateral vestibular lesion	5 cases
C.—Symptoms absent both ears, 2 cases	Unilateral vestibular lesion	2 cases

VIII.—*Deafness (Objective); methods.*

Hearing was tested in all cases by the whispered voice and watch by a single observer. The same testing room was used throughout, with a low and fairly constant noise-level. Pure tone audiometric tests were also carried out with a Marconi Ekco audiometer in a sound proof room. All Weber and Rinné tests were performed with a single 512 cycle fork of the Gardiner-Brown type. The whisper used was normally heard at 30 ft., and the assessment of objective deafness was based entirely upon the results of this test. A reduction of the hearing distance to 20 ft. was regarded as the minimal degree of deafness which could be taken as significant, and is referred to as slight deafness in the following scale which has been adopted. The symbols D. (Sl), D.(M), &c. will be freely used in the further parts of the text.

Slight deafness, D.(Sl.).—20 ft. and less. Greater than 10 ft.
Moderate deafness, D.(M.).—10 ft. and less. Greater than 2 ft.
Severe deafness, D.(S.).—2 ft. and less.
Very severe deafness, D.(V.S.).—Just heard at meatus.
Complete deafness, D.(C.).—Loud voice not heard at meatus with the other ear excluded by masking.

The term deafness as used alone in the text refers only to the results of the whisper test. Deficiency of cochlear function revealed by the watch or audiometer will be so specified.

Masking.—In severe unilateral deafness of the internal ear type it is essential when testing the deafer ear to exclude perception by the opposite ear by means of a suitable masking noise. Certain limits require to be observed in respect of the intensity and frequency characteristics of such a noise if it is to be effective. In addition, it is essential that its action should be limited to the masked ear. The noise of a Bárány noise apparatus is intermittent in character and also spreads by air conduction to the opposite ear and we have found it most unsuitable for use as a masking device. Valve hiss amplified and applied to the ear by means of a close fitting receiver has been found an exceedingly effective if elaborate procedure. Results as good have been obtained with much greater convenience by means of a speaking tube type of hearing aid with a long flexible tube. The masking noise consists of a sh— sound delivered by an assistant into the mouthpiece which is held tightly over his mouth, while the observer carries out the test. The intensity and frequency characteristic of the sound reaching the ear give it a high masking efficiency, while the speaking tube limits it to the masked ear.

IX.—*Deafness (Objective).*

The degree of deafness revealed by tests in the 50 cases and its distribution between the ears is analysed in the following table which is based essentially upon the results of the whisper test. The numbers given are of the cases as they are listed in the Appendix. (N.) denotes that the caloric reactions were normal, and * that the caloric reactions showed a vestibular abnormality on the side of the *better* hearing ear. In the absence of a symbol the caloric reactions showed a vestibular abnormality on the side of the worse hearing ear.

GROUP I.	
6 cases of D.(C.) in one ear. Hearing in opposite ear	D.(M.) 5 cases (22,* 26, 29, 36, 45) D.(Sl.) 1 case (47)
Cochlear deficiency BILATERAL IN 6 CASES.	
GROUP II.	
7 cases of D.(V.S.) in one ear. Hearing in opposite ear	D.(S.) 1 case (49(N.)) D.(M.) 1 case (7) D.(Sl.) 3 cases (5, 31, 48(N.)) N. 2 cases (8, 30) (Of these, 1 (30) showed loss to the audiometer and watch)
Cochlear deficiency BILATERAL IN 6 CASES. *Unilateral in 1 case* (8).	

GROUP III.

8 cases of D.(S.) in one ear. Hearing in opposite ear { D.(M.) 2 cases (37,* 38); D.(Sl.) 3 cases (13,* 35, 39); N. 3 cases (14, 15, 34) (Of these 2 (14, 15) showed loss to watch and audiometer)

Cochlear deficiency BBILATERAL IN 7 CASES. *Unilateral in* 1 *case* (34).

GROUP IV.

10 cases of D.(M.) in one ear. Hearing in opposite ear { D.(Sl.) 6 cases (9, 10,* 18, 28, 46, 50(N.)); N. 4 cases (20, 21, 24, 25) (Of these, 2 (20, 21) showed loss to the audiometer)

Cochlear deficiency BILATERAL IN 8 CASES. *Unilateral in* 2 *cases* (24, 25).

GROUP V.

4 cases of D.(Sl.) in one ear. Hearing in opposite ear N. (3,* 27, 33, 42) (Of these, 2 (33, 42) showed loss to the watch and audiometer)

Cochlear deficiency BILATERAL IN 2 CASES. *Unilateral in* 2 *cases* (3, 27).

GROUP VI.

6 cases of D.(Sl.) in both ears.

Loss to the watch, audiometer or both was unequal in the two ears in 3 cases(1, 2 and 11) and equal in 3 cases (6, 23, 41).

Cochlear deficiency BILATERAL IN 6 CASES.

GROUP VII.

7 cases of Normal (N.) hearing in both ears, but with a history of tinnitus in one or both ears.

In 6 cases there was bilateral loss to the watch, audiometer, or both. The loss was unequal in the two ears in 3 cases (17, 32, 44) and equal in 3 cases (12, 16, 19).

In 1 case (40) there was unilateral loss to the watch and audiometer.

Cochlear deficiency BILATERAL IN 6 CASES. *Unilateral in* 1 *case* (40).

GROUP VIII.

2 cases of Normal (N.) hearing in both ears without a history of tinnitus or deafness.

Both showed bilateral loss to the watch and audiometer.

The loss was unequal in the two ears in 1 case (4) and equal in 1 case (43).

Cochlear deficiency BILATERAL IN 2 CASES.

Conclusions.

(1) Cochlear deficiency.

Evidence of cochlear deficiency was evident in all of the 50 cases.

In 43 cases it was bilateral.

In 7 cases it was unilateral.

(2) Vestibular deficiency.

The caloric reactions were normal in 3 cases and abnormal in 47 cases.

Of the 35 cases in Groups I to V in which the hearing loss for the whisper was at least slight and unequal in the two ears, the caloric tests showed a vestibular lesion of the deafer ear in 27 cases. In 5 cases (3, 10, 13, 22, 37) a vestibular lesion was indicated of the better hearing ear. In the remaining 3 the reactions were normal.

Of the 15 cases of Groups VI, VII and VIII in which the hearing loss for the whisper was slight and equal, or absent, watch and audiometer tests showed inequality of hearing in 7 cases (1, 2, 4, 11, 17, 32, 44), and in all of these the caloric tests showed a vestibular lesion of the worse hearing ear. Of the remaining 8 cases there were 7 with equal hearing for whisper, watch and audiometer and in all of these a unilateral vestibular lesion was present (6, 12, 16, 19, 23, 41, 43).

In all, there were: 35 cases with unequal hearing with a vestibular lesion of the worse hearing ear; 5 cases with unequal hearing with a vestibular lesion of the better hearing ear; 3 cases with unequal hearing with no vestibular lesion; 7 cases with equal hearing and a unilateral vestibular lesion.

X.—*The character of the deafness as revealed by the Rinné and Weber tests.*

These tests were carried out in 49 of the 50 cases, and in 45 of these the results fall into 3 well-defined groups:

Group I.	Rinné + in both ears	25 cases.
Group II.	Rinné + in one ear. False − in the other ...	18 cases.
Group III.	Rinné + in one ear. True − in the other ...	2 cases.

Group I.—In 14 of the 25 cases of this group hearing for the whisper was equal and good in the two ears, N. or D(Sl.), though slight differences of hearing for the watch or audiometer were revealed in 7 cases. In 9 of these 14 cases the Weber was not referred.

Group II.—In 12 cases of this group hearing for the whisper was unequal in the two ears and severe or worse in the worse hearing ear. The Rinné test was false − in this ear and in 10 cases the Weber was referred to the

other. In all of these the false nature of the – response to the Rinné test was revealed only by the use of a masking noise in the better hearing ear.

Group III.—Both cases of this group (5 and 9) were typical examples of unilateral conducting deafness. In both there was gross tympanic damage in the ear with the – Rinné and the Weber was referred thereto.

The results of the Rinné and Weber tests show in the great majority of cases that the deafness is of the internal ear type. Reactions indicative of a conducting type of lesion are associated with gross tympanic lesions. These occur rarely.

XI.—*Occurrence of tympanic lesions and Eustachian efficiency.*

A. Tympanic lesions.—In 6 cases there was evidence of unilateral tympanic damage due to old suppuration. In one case both tympana were affected. Active suppuration was never observed.

Unilateral.—In two cases (5 and 9) the damage was severe; it consisted of gross scarring of the membrane in one, and its total defect in the other. Both cases showed a typical conducting deafness in the ear with the tympanic changes with reference thereto of the Weber, and a – Rinné test. In both cases there was also evidence of internal ear deafness of the opposite ear.

In four cases there was a less pronounced defect of one tympanum consisting either of scarring of the membrane or of an old healed perforation. In all there was severe or complete internal ear deafness of the ear showing the tympanic lesions, with reference of the Weber to the opposite ear.

Bilateral.—In the one case (14) there was bilateral scarring of the tympanic membranes, with internal ear deafness of both ears. Tympanic lesions were therefore present in only 7 of the 50 cases. In all except 2 in which the lesions were gross the deafness was of the internal ear type.

B. Eustachian efficiency.—The conventional tests of Eustachian efficiency by means of auscultation during auto-inflation or inflation with a Politzer bag or Eustachian catheter have been extensively applied by us to cases of Ménière's disease not included in the present series. In the absence of collateral evidence in the shape of conducting deafness and membrane retraction we have found it difficult to believe that useful information concerning the functional efficiency of the Eustachian tube is often provided by these tests. Such collateral evidence has rarely been obtainable in the present cases and the tests have accordingly not been systematically applied. In agreement with Crowe and Wright we believe

that the findings in these cases strongly contradict the view that tympanic disease or Eustachian obstruction play a significant part in the ætiology of Ménière's disease. This in no way invalidates the well-known clinical observations of Sydney Scott and others of the dramatic relief of vertigo by Eustachian inflation. The endolymphatic distension which is found to occur in Ménière's disease would clearly render the labyrinth very sensitive to an inwards displacement of the stapes resulting from Eustachian obstruction, and the situation then arising would as clearly be open to dramatic relief by Eustachian catheterization. The point has already been discussed by Hallpike and Cairns (1938).

XII.—*Audiograms.*

Pure tone audiometer tests were carried out in 47 of the 50 cases. The curves have been studied with a view to revealing any particular form which might be regarded as characteristic of Ménière's disease in at any rate one of its stages. The audiograms fall into three distinct classes.

(1) A variety with both curves sloping down towards the right, thus indicating a selective high tone loss. The slope of the curves varies widely as also their level and distance apart. There were 18 audiograms of this type.

(2) A variety with both curves roughly horizontal, indicating the absence of a selective tonal loss. There is wide variation in the level and distance apart of the curves. There were 23 audiograms of this type.

(3) A combined variety in which each ear shows one of the two types of curve described. There were 6 audiograms of this type.

From this it is concluded that there is no particular type of audiometric curve which can be regarded as characteristic of Ménière's disease at any of its stages.

There were 9 cases in which hearing for the whisper was normal in both ears. In 8 a bilateral loss was revealed by the audiometer in the audiogram, and in the majority of these by the watch test also. In addition there were 13 cases in which the hearing for the whisper was normal in one ear only; 7 showed a loss of hearing in this ear for both audiometer and watch. The audiometer is thus shown to be of value in revealing the presence of slight losses when hearing for the whisper is normal, though it may be added that in the majority of cases the same purpose is well served by the watch tests. This should not obscure the great value of the audiometer in providing accurate records of changes in hearing over a wide range of tones observed in the course of treatment.

XIII.—*Diagnosis, treatment and results.*

Diagnosis seldom presents difficulties. It is based upon the presence of the well-known and characteristic combination of paroxysmal vertigo, internal ear deafness and (usually) tinnitus, which has been described before by others and verified in the present series of patients. Absence of other neurological signs make it difficult to confuse with lesions of the 8th nerve or the central nervous system. Thus, in tumour of the 8th nerve, the vertigo is usually a less dominant feature. Sensory disturbance in the trigeminal field is common and changes in the protein content of the C.S.F. almost invariable.

In disseminated sclerosis with intermittent giddiness involvement of the cochlear apparatus with resultant deafness is rare, while other clinical features associated with involvement of the long tracts and ocular nuclear connections are common.

In syringobulbia and tumours involving the brain-stem a variety of other gross neurological signs are nearly always present. Syphilitic disease of the labyrinth as also its involvement by blood-borne pyogenic organisms has been observed, e.g. in the course of an osteomyelitis of the tibia. The diagnosis of these conditions from Ménière's disease is sometimes difficult and will be discussed more fully in a subsequent publication.

The great majority of the patients included in the present series have been under observations for more than six months, and many for more than 2 years. In nearly all, the diagnosis was made at the first examination, and has required revision in none.

Treatment.	Effect upon Vertigo.				
	Abolished	*Much diminished*	*Diminished*	*Unchanged*	*Increased*
Phenobarbital .. (In 2 cases bromide was also given and in 1 case pilocarpine)	Nil	1, 11, 23, 42, 48*	3, 5, 6, 12, 13, 16, 21, 22, 24, 29, 37, 40, 43, 45*	9†, 26, 31	32‡, 44
Labyrinthectomy..	8, 14, 35, 36	2, 18, 25, 34	15		
Incision of saccus endolymphaticus	33	50			

* Antral drainage or lavage.
† Tonsillectomy.
‡ Restriction of fluid and salt as In-patient.

Summary.

Of 24 cases treated with phenobarbital, the vertigo was abolished in none, much diminished in 5, diminished in 14, unchanged in 3 and increased in 2.

Of 9 cases treated by unilateral labyrinthectomy, the vertigo was abolished in 4, much diminished in 4, and diminished in 1.

Of 2 cases treated by unilateral incision of the saccus endolymphaticus, the vertigo was abolished in 1 and much diminished in the other.

Comment.

Treatment by phenobarbital alone gives satisfactory results in the majority of cases, although abolition of the vertigo has not been observed. Unilateral labyrinthectomy, on the other hand, led to abolition of the vertigo in 4 of 9 cases. In 4 cases the vertigo was much diminished, and in one case diminished.

Following incision of the saccus endolymphaticus vertigo was abolished in 1 case and much diminished in the other.

Conclusion.

Abolition or great diminution of vertigo is much more likely to be achieved by labyrinthectomy carried out in suitable cases than by the use of phenobarbital. The technique of and indications for labyrinthectomy and other surgical measures for the treatment of Ménière's disease will be more fully discussed in a separate publication.

XIV.—*Summary and Comments, Section I.*

So far as the present analysis has gone the clinical picture of Ménière's disease corresponds closely with that given by Gowers, Crowe and others. The clinical findings again stress that the nature and course of the symptoms and signs of this disorder are highly characteristic and so warrant the view so well emphasized by Crowe and Wright that they result from a disease *sui generis* of the labyrinth. A striking feature of the present analysis is the finding of bilateral loss of cochlear function in no less than forty-three of the fifty cases, whilst in forty-seven there were unilateral abnormalities of the caloric reactions. In thirty-five of these the side of the vestibular lesion coincided with that of the worse hearing ear and in five with that of the better hearing ear. The character of the abnormalities of the caloric reactions and their interpretation will be discussed in the succeeding section.

SECTION II.—RESULTS AND SIGNIFICANCE OF THE CALORIC REACTIONS.

A.—Results of caloric reactions.

B.—Correlation of results of cochlear and vestibular tests.

C.—Discussion.

A.—*Results of caloric reactions.*

The normal pattern of the caloric reactions obtained with the present technique has been described in the first paper of this issue (fig. 1) and is shown again for reference in fig. 1. In three cases only of the present

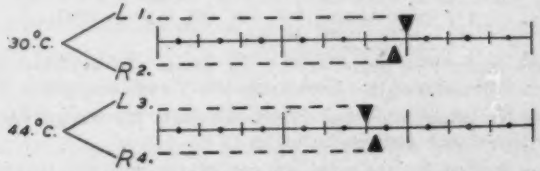

FIG. 1.—Normal.

series (48, 49, 50) were the caloric reactions of this normal pattern. Two types of disturbance in this pattern observed in a few cases of Ménière's disease have been described in the preceding paper. They are believed for reasons given therein to be characteristic respectively of unilateral paresis of the utricle and external canal.

I. *Utricular paresis. In* 10 *cases of the present series the abnormalities were of this type. Appendix Class I.*

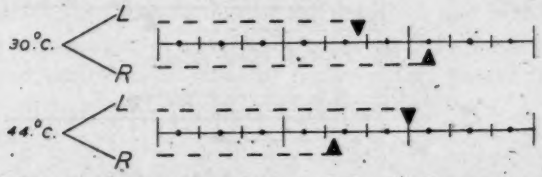

FIG. 2.—Directional preponderance to the left. (Right utricular paresis.)

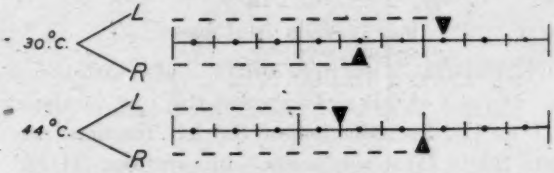

FIG. 3.—Directional preponderance to the right. (Left utricular paresis.)

Fig. 2 shows the type of disturbance in this normal pattern associated with right utricular paresis. It has been described (p. 122) as directional preponderance of caloric nystagmus to the left, and shows an increase of reactions 2 and 3 (nystagmus to the left) with respect to reactions 1 and 4 (nystagmus to the right). (More precisely, reactions 2 and 3 are exaggerated and reactions 1 and 4 diminished.) Three cases in the present series showed this type of abnormality. In two (1, 2) the disturbance was moderate. In one (9) it was severe, with elimination of reaction 1 and 4. Fig. 3 shows the type of disturbance associated with left utricular paresis. It has been described (p. 122) as directional preponderance of caloric nystagmus to the right, and shows an increase of reactions 1 and 4 (nystagmus to the right) with respect to reactions 2 and 3. (More precisely, reactions 1 and 4 are exaggerated and reactions 2 and 3 diminished.) Seven cases in the present series showed this type of abnormality. In six (3 to 8) the disturbance was moderate. In one (10) it was severe, with elimination of reactions 2 and 3.

II. *Canal paresis. In 29 cases of this series the abnormalities were of this type. Appendix Class II.*

Fig. 4 shows the type of disturbance associated with *left* canal paresis. Both cold and hot reactions (1 and 3) of the left canal show an equal

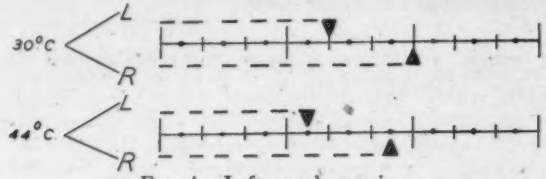

FIG. 4.—Left canal paresis.

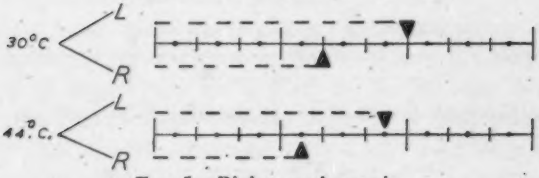

FIG. 5.—Right canal paresis.

reduction. The reactions of the right canal (2 and 4) maintain their normal relationship. 15 cases of this series showed this type of abnormality. In five cases (11 to 15) the reduction of the left reactions was moderate. In seven cases (19 to 25) it was severe. In two cases (31 and 32) it was very severe. By this is meant that no responses were obtained from the left canal by means of the normal hot and cold stimuli. A response was obtained following prolonged stimulation at 18° C. In one case (37) there was complete loss of the left reactions even to prolonged stimulation at 18° C.

Fig. 5 shows the type of disturbance associated with *right* canal paresis. Both hot and cold reactions of the right canal (2 and 4) show equal reduction. The reactions of the left canal (1 and 3) maintain their normal relationship. Fourteen cases of this series showed this type of abnormality. In three cases (16 to 18) the reduction of the right reactions was moderate. In five cases (26 to 30) it was severe. In four cases (33 to 36) it was very severe and in two (38 and 39) it was complete.

III. *Utricular and canal paresis in combination. Appendix Class III.*

In a further group of eight cases the pattern of the caloric reactions has not been typical of either canal or utricular paresis as already identified. Further consideration makes it possible to regard the reaction patterns of this group as being due to combinations in varying proportions of these two elements, i.e. canal paresis with concomitant paresis of the utricle on the same side.

In four of these cases the canal paresis element was dominant, i.e. both cold and hot reactions of one ear were very severely reduced or completely eliminated, so indicating a very severe or complete loss of canal function. In addition, a concomitant paresis of the homolateral utricle was revealed by the finding of a directional preponderance of nystagmus to the opposite side as shown by an exaggeration in the hot response of the opposite ear. In three of these cases (44 to 46) the left canal and utricle were so affected, and in one (47) the right canal and utricle. The reaction patterns of Cases 45 and 47 are shown in figs. 6 and 7 and are particularly reminiscent of the results observed after unilateral labyrinthectomy and described in detail in the preceding paper. In this connection the suppression of the left cold reaction in Case 47 is particularly noteworthy.

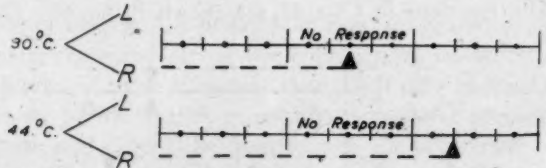

FIG. 6 (*Case 45*).—Combined *left* utricular and canal pareses. (Canal paresis dominant.)

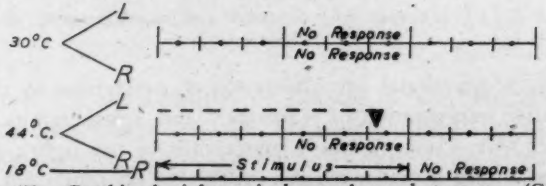

FIG. 7 (*Case 47*).—Combined *right* utricular and canal pareses. (Canal paresis dominant.)

In a further four cases the elements of canal and utricular paresis were both present. Neither was dominant and the resulting disturbance of the reaction pattern was more difficult to interpret. In two cases (40 and 41) the left utricle and canal were affected. The reactions in Case 40 are shown in fig. 8. Their general type reveals a directional preponderance

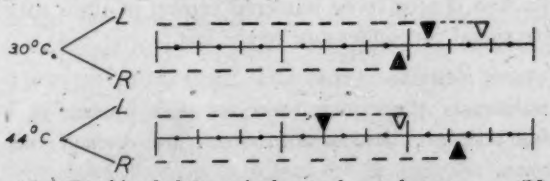

FIG. 8 (*Case 40*).—Combined *left* utricular and canal pareses. (No dominant element.)

of nystagmus to the right, i.e. with a relative exaggeration of reactions 1 and 4 (nystagmus to the right) with respect to reactions 2 and 3 (nystagmus to the left) and is thus indicative of a left utricular paresis. There is also a further asymmetry of the pattern which is particularly conspicuous in the very large disproportion between reactions 3 and 4. This additional asymmetry is most readily explicable as being the result of a concomitant paresis of the left canal. The matter is best explained by eliminating the results of such a supposed canal lesion by introducing into the pattern of the responses proportionate increases in the cold and hot reactions of the left canal (reactions 1 and 3 as shown by the dotted lines . . . ▽ in fig. 8, when the pattern is then seen to be rendered typical of left utricular paresis alone. (Directional preponderance to the right.)

In two cases (42 and 43) the right utricle and canal were similarly affected. The reactions in Case 42 are shown in fig. 9. Their general

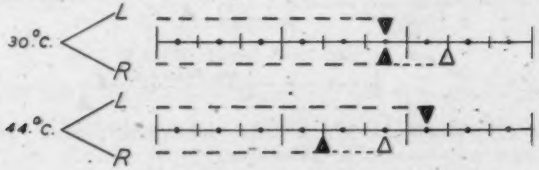

FIG. 9 (*Case 42*).—Combined *right* utricular and canal pareses. (No dominant element.)

type reveals a directional preponderance of nystagmus to the left, i.e. with a relative exaggeration of reactions 2 and 3 (nystagmus to the left) with respect to reactions 1 and 4 (nystagmus to the right); and is thus indicative of a right utricular paresis. A further asymmetry of the pattern is conspicuous in the very large disproportion between reactions 3 and 4, which would again seem most readily explicable as being the result of a concomitant paresis of the right canal. As before, the matter is best explained by eliminating the results of such a supposed lesion by introducing into the diagram proportionate increases in the cold and hot reactions of the right canal as shown by the dotted lines . . . △ in fig. 9 when the pattern is seen to be rendered typical of right utricular paresis alone. (Directional preponderance to the left.)

B.—*Summary of Results.*

Abnormalities of the caloric reactions were present in 47 of the 50 cases of this series. These abnormalities are divided into three well defined classes.

Class I.—Unilateral utricular paresis, 10 cases.

A. Left utricle, 7 cases.

B. Right utricle, 3 cases.

Class II.—Unilateral canal paresis, 29 cases.

A. Left canal, 15 cases.

B. Right canal, 14 cases.

Class III.—Unilateral utricular and canal paresis in combination, 8 cases.

A. Canal paresis dominant, 4 cases { left, 3. / right, 1.

B. No dominant element, 4 cases { left, 2. / right, 2.

It is necessary to stress the probable fallacy which attends our description as unilateral of many of the vestibular lesions tabulated above. In some, at any rate, of these it is clear that the results of the caloric tests might as readily be interpreted as revealing unilateral preponderance of bilateral lesions; and indeed the frequency in the occurrence of bilateral loss of cochlear function makes this the more likely. The impossibility of obtaining an absolute measure of the normal caloric response renders closer analysis impossible.

C.—Discussion.

Apart from the abnormalities of the caloric reactions, the clinical findings in the present series of cases certainly emphasizes a little known feature of this disorder, namely the bilateral distribution of the cochlear changes. Regarding the frequency of occurrence of deafness, Crowe (1938) found deafness in all but 5 of 145 patients, a figure which is in substantial agreement with our own results. Regarding its bilaterality, however, he describes the deafness as usually confined to one ear and states in fact that in 90 per cent. of his cases the disease was unilateral. In our own series there was bilateral cochlear involvement in forty-three cases, or 86 per cent., although to be sure in the majority of these the deafness was more pronounced in one ear than the other, in which it often required demonstration by the whisper or other tests. Wright (1938) observed bilateral deafness in 50 per cent. of his cases. Our own findings reveal a still higher incidence and we regard them as indicative of the essentially bilateral character of the disease. It is of interest also to note that in thirty-five of our forty-three cases, patients in whom the hearing loss was more pro-

nounced, or present only in one ear, the caloric reactions showed a vestibular lesion on the side of the worse hearing ear. From this it seems reasonable to believe that the disease usually affects one labyrinth in advance of the other, and that cochlear and vestibular damage are usually associated therein. Here again, however, the essentially bilateral distribution of the labyrinthine changes is stressed by the finding in five patients of a vestibular lesion in the better hearing ear.

The abnormalities in the caloric responses which have been described invite particular discussion in respect of their frequency of occurrence and character. Regarding the frequency with which we have observed abnormalities in the caloric reactions it may be noted that Crowe, using different methods, found the caloric reactions normal in 35 per cent. of his patients, and for this reason among others questioned the paretic nature of the labyrinthine lesions. In the present series the caloric reactions have been found normal in only 6 per cent., and this is probably indicative of the increased efficiency of the caloric tests attainable by means of the technique which has been described. With regard to the character of the abnormalities of the caloric responses now described it will be recalled that two definite types of abnormality in the pattern of the responses have been described in the preceding papers, and the hypothesis put forward, on grounds in part of theory, that these should be regarded as diagnostic respectively of paretic lesions of the utricle and external canal.

Regarding the first of these abnormalities, the phenomenon of directional preponderance, it is of interest to note that Vogel in 1929 clearly describes its occurrence in a number of cases of Ménière's disease. He relates it, however, to the same phenomenon recognized by de Kleyn and de Barenne as being due to cerebral lesions and for this reason considers its occurrence to be evidence of the location within the central nervous system of the lesion concerned. The validity of our own hypothesis is certainly supported by the results of the caloric tests in the present series of cases. Firstly, by the fact that the *only* abnormalities observed conform very closely with the two types described, occurring usually separately and sometimes in combination. Secondly, by the fact that they occur in association with a labyrinthine disorder of which the lesions, essentially paretic, are of uncertain distribution and may well involve either the external canal, utricle or both. If upon these grounds it can be considered justifiable to apply the hypothesis to the interpretation of

the caloric reactions in this series, it would seem reasonable to conclude that in the majority of cases of Ménière's disease there occurs a lesion of the external canal without utricular involvement. In a considerable number (about 20 per cent.), utricular paresis occurs alone, and nearly as often in combination with a paresis of the external canal.

Summary.

(1) A detailed analysis is given of the clinical findings in 50 cases of Ménière's disease, including the results of audiometric and caloric tests.

(2) The results support the views of Crowe and Wright that the clinical condition is sufficiently characteristic to justify its attribution to some specific type of labyrinthine disorder. The findings are also in general accord with the picture of the anatomical changes revealed within the labyrinth in other cases of Ménière's disease by Hallpike, Cairns, Wright and Rollin.

(3) Loss of cochlear function was observed in all cases and in 86 per cent. of cases it was bilateral, and the essentially bilateral character of the disease process is accordingly stressed. The deafness was nearly always of the internal ear type. No evidence is found in support of the view that tympanic disease or oro-nasal foci of infection play an important role in the ætiology of the disorder.

(4) The caloric reactions showed the presence of a vestibular lesion in forty-seven of the fifty cases. In the majority of these the vestibular lesion was on the side of the worse hearing ear. In five cases, however, the vestibular lesion was on the side of the better hearing ear.

(5) The abnormalities of the caloric reactions have been interpreted in accordance with principles developed in the preceding papers.

(6) As so interpreted they are considered to indicate the occurrence of three well defined types of unilateral vestibular lesion: (1) Paretic lesions of the utricle (10 cases); (2) paretic lesions of the external canal (29 cases); (3) paretic lesions of the utricle and external canal occurring in combination (8 cases).

Our thanks are due to the staff of the National Hospital for their kindness in allowing us to examine patients under their care and to Dr. E. Arnold Carmichael (Director of Research) for his helpful criticism.

The work was carried out on behalf of the Medical Research Council.

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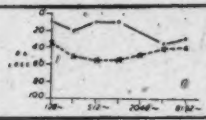
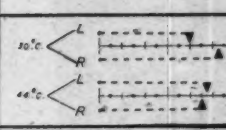
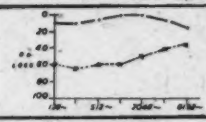
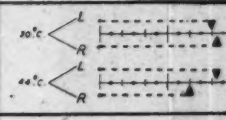
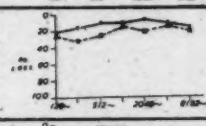
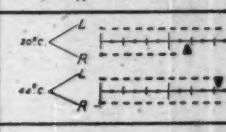
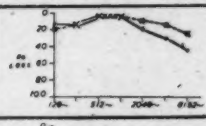
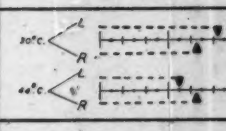
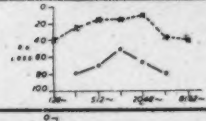
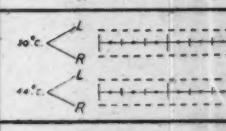
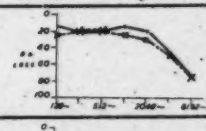
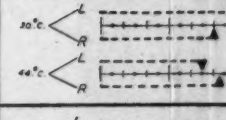
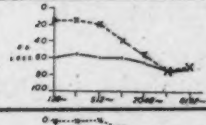
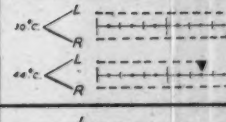
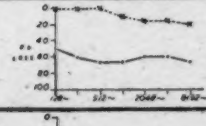
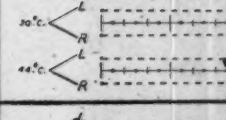
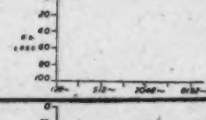
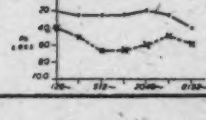
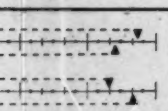
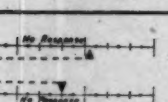
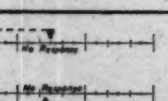
APPENDIX.

Note.—Abbreviation, Column 11. "N.H." for "not heard."

CLASS I. Directional preponderance alone. 10 cases.

	1	2	3	4		5	6	7	8	9		10		11		12		13		
	Case No.	Sex	Age	Tinnitus (T) Deafness (D) Duration in years		Vertigo. Duration in years	Nausea (N) Vomiting (V) Headache (H) with Vertigo	Mode of Onset of Vertigo	Clinical Evidence of Oro-nasal Sepsis	Tympanic Membranes		Whisper. N. 30 ft.		Watch. N. 18 in.		Rinné 512~		Weber 512~		
				Left	Right					Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	
Moderate to Left	W.M. 1	♂	43	Nil	T. $\frac{4}{12}$ D. $\frac{4}{12}$	$\frac{4}{12}$	V.	Rapid. Preceded by feeling of fullness of right ear	Nil. X-rays negative	N.	N.	20 ft.	15 ft.	9 in.	3 in.	+	false –		→	
	E.T. 2	♀	32	Nil	T. 3	3	N.	No note	Nil. X-rays negative	N.	N.	20 ft.	16 ft.	1 ft.	3 in.	+	+	←	→	
Moderate to Right	D.H. 3	♀	36	Nil	T. $\frac{2}{12}$ D. $\frac{2}{12}$	$\frac{2}{12}$	No note	No note	Nil. No X-rays	N.	N.	>20 ft.	20 ft.	18 in.	6 in.	+	+		→	
	L.M. 4	♀	43	Nil	Nil	$\frac{4}{12}$	V.	Rapid. No aura	Nil. No X-rays	N.	N.	>20 ft.	>20 ft.	At meatus	3 in.	+	+	←	→	
	O.P. 5	♂	54	D.4	Nil	3	Nil	Slow. Preceded by visual disturbance	Nil. No X-rays	Severe scarring	N.	At meatus	20 ft.	N.H.	N.H.	–	+	←		
	S.E. 6	♂	50	T.3 D.3	T.3 D.3	3	N. V.	Rapid. No aura	Nil. X-rays negative	N.	N.	20 ft.	20 ft.	N.H.	N.H.	+	+	←	→	
	T.H. 7	♂	65	D.2	Nil	$\frac{3}{12}$	N. V.	Rapid. No aura	Nil. X-rays negative	N.	N.	At meatus	4 ft.	N.H.	N.H.	+	+		→	
	M.B. 8	♀	46	D.20	T. 19	3	N. V. H.	Rapid. No aura	Nil. X-rays negative	N.	N.	At meatus	>20 ft.	N.H.	12 in.	false –	+		→	
Severe to Left	E.G. 9	♀	43	Nil	T. $\frac{6}{12}$ D. $\frac{6}{12}$	$\frac{3}{12}$	N. V.	Slow. Preceded by numb feeling in right ear	Infected tonsils No X-rays	Opaque	Total defect. Dry.	18 ft.	4 ft.	15 in.	N.H.	+	–		→	
Severe to Right	W.C. 10	♂	42	Nil	T.10 D10.	$\frac{4}{12}$	N.	No note	Nil. X-rays negative	N.	N.	20 ft.	3 ft.	6 in.	At meatus	+	false –	←		

9		10		11		12		13		14	15
Tympanic Membranes		Whisper. N. 30 ft.		Watch. N. 18 in.		Rinné 512~		Weber 512~		Audiogram	Caloric Tests
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right		
N.	N.	20 ft.	15 ft.	9 in.	3 in.	+	false −				
N.	N.	20 ft.	16 ft.	1 ft.	3 in.	+	+				
N.	N.	>20 ft.	20 ft.	18 in.	6 in.	+	+				
N.	N.	>20 ft.	>20 ft.	At meatus	3 in.	+	+				
Severe scarring	N.	At meatus	20 ft.	N.H.	N.H.	−	+				
N.	N.	20 ft.	20 ft.	N.H.	N.H.	+	+				
N.	N.	At meatus	4 ft.	N.H.	N.H.	+	+				
N.	N.	At meatus	>20 ft.	N.H.	12 in.	false −	+				
Opaque	Total defect. Dry.	18 ft.	4 ft.	15 in.	N.H.	+	−				
N.	N.	20 ft.	13 ft.	6 in.	At meatus	+	false −				

15	16			17	18
ric Tests	Summary of Results of Functional Tests			Treatment	Results
	Cochlear		Caloric		
	Left	Right			
	D. (Sl.)	D. (Sl.)	Directional preponderance to left	Phenobarbital	Vertigo much diminished
	D. (Sl.)	D. (Sl.)	,,	Right labyrinthectomy	Vertigo much diminished Tinnitus increased
	N.	D. (Sl.)	Directional preponderance to right	Phenobarbital	Vertigo diminished
	N.	N.	,,	Phenobarbital	No note
	D. (V.S.)	D. (Sl.)	,,	Phenobarbital	Vertigo slightly diminished
	D. (Sl.)	D. (Sl.)	,,	Phenobarbital	Vertigo diminished
	D. (V.S.)	D. (M.)	,,	Phenobarbital	No note
	D. (V.S.)	N.	,,	Left labyrinthectomy	Vertigo abolished Tinnitus in left ear
	D. (Sl.)	D. (Mod.)	Severe directional preponderance to left	Tonsillectomy Phenobarbital and bromide	Vertigo unchanged
	D. (Sl.)	D. (M.)	Severe directional preponderance to right	No note	No note

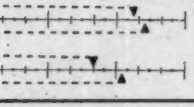
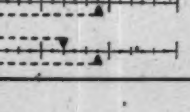
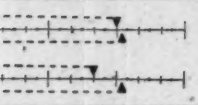
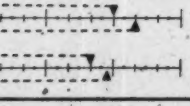
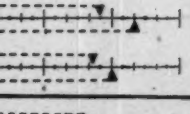
CLASS II. Canal paresis alone. 29 cases. Group 1—Moderate, 8 cases. Group 2—Severe, 12 cases. Group

	1	2	3	4		5	6	7	8	9		10		11		12		13		
	Case No.	Sex	Age	Tinnitus (T) Deafness (D) Duration in years		Vertigo. Duration in years	Nausea (N) Vomiting (V) Headache (H) with Vertigo	Mode of Onset of Vertigo	Clinical Evidence of Oro-nasal Sepsis	Tympanic Membranes		Whisper N. 30 ft.		Watch N. 18 in.		Rinné 512~		Weber 512~		Aud
				Left	Right					Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	
GROUP 1 Moderate	E.D. 11	♀	51	T.1. D.1.	T. recently	7	Notes incomplete	Slow. No aura	Nil No X-rays	N.	N.	15 ft.	20 ft.	3 in.	3 in.	+	+			
	W.G. 12	♂	42	T.$\frac{4}{12}$	T.$\frac{4}{12}$	$\frac{4}{12}$	N. V.	Rapid. Preceded by increase of tinnitus.	Nil. X-rays negative	N.	N.	> 20 ft.	>20 ft.	3 in.	2 in.	+	+			
	E.M. 13	♀	54	Nil	D. 39	$\frac{?}{12}$	N. V.	Rapid. No aura	Nil. No X-rays	N.	N.	15 ft.	1 ft.	N.H.	N.H.	±	−			
	H.H. 14	♂	42	T.5. D.10	Nil	$\frac{6}{12}$	N. V.	Rapid. No aura	Nil. X-rays negative	Scarring	Scarring	1 ft.	>20 ft.	N.H.	6 in.	false −	+			
	E. L. 15	♀	45	T.5 D.$\frac{11}{12}$	Nil	$\frac{11}{12}$	N. V.	Rapid. No aura	Nil. X-rays negative	Retracted and Opaque	N.	1 ft.	>20 ft.	N.H.	4 in.	false −	+			
	M.A. 16	♀	20	T.2	T. 2	2	N. H.	Slow. Preceded by increase of tinnitus	Nil. X-rays negative	N.	N.	>20 ft.	> 20ft.	7 in.	7 in.	+	+			
	H.G. 17	♀	43	Nil	T.$\frac{?}{12}$	$\frac{?}{12}$	Nil	Slow. No aura	Nil. X-rays negative	N.	N.	>20 ft.	>20 ft.	1½ ft.	N.H.	+	+			
	G.A. 18	♂	38	Nil	D.2	1½	N. V.	Rapid. No aura	Nil. X-rays negative	N.	N.	20 ft.	5 ft.	2 in.	N.H.	+	±			
GROUP 2 Severe	D.B. 19	♀	24	T. ? Duration	T.	2	Nil	Slow. No aura	Nil X-rays negative	N.	N.	>20 ft.	>20 ft.	12 in.	12 in.	+	+			
	S.C. 20	♀	37	T.5½ D.5½	Nil	6	N. V.	Rapid. No aura	Nil. No X-rays	N.	N.	8 ft.	>20 ft.			+	+			

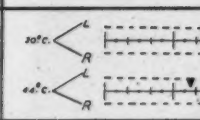
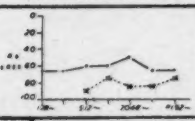
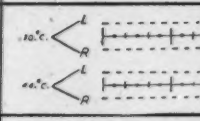
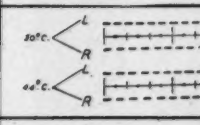
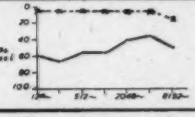
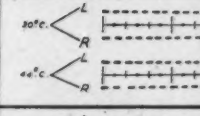
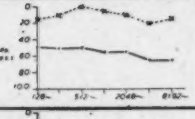
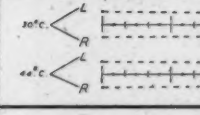
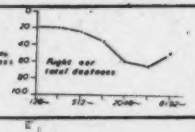
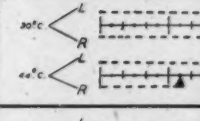
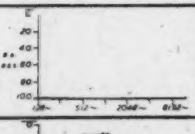
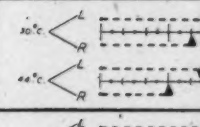
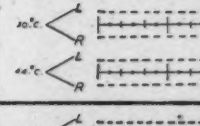
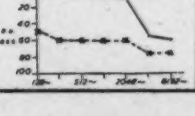
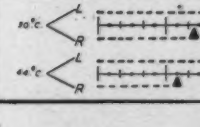
ate, 8 cases. Group 2—Severe, 12 cases. Group 3—Very Severe, 6 cas

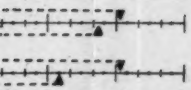
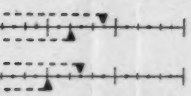
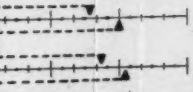
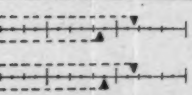
9		10		11		12		13		14	15
Tympanic Membranes		Whisper N. 30 ft.		Watch N. 18 in.		Rinné 512~		Weber 512~		Audiogram	Caloric Tests
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right		
N.	N.	15 ft.	20 ft.	3 in.	3 in.	+	+				
N.	N.	> 20 ft.	>20 ft.	3 in.	2 in.	+	+				
N.	N.	15 ft.	1 ft.	N.H.	N.H.	±	−				
rring	Scarring	1 ft.	>20 ft.	N.H.	6 in.	false −	+				
rac- and aque	N.	1 ft.	>20 ft.	N.H.	4 in.	false −	+				
N.	N.	>20 ft.	> 20ft.	7 in.	7 in.	+	+				
N.	N.	>20 ft.	>20 ft.	1½ ft.	N.H.	+	+				
N.	N.	20 ft.	5 ft.	2 in.	N.H.	+	±				
N.	N.	>20 ft.	>20 ft.	12 in.	12 in.	+	+				
N.	N.	8 ft.	>20 ft.			+	+				

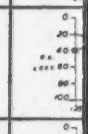
6 cases. **Group 4—Complete, 3 cases.**

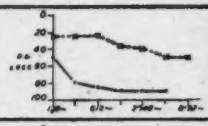
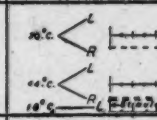
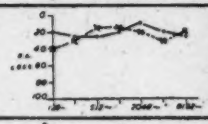
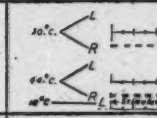
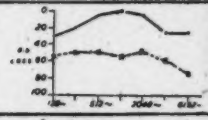
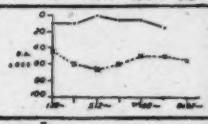
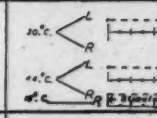
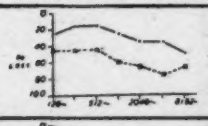
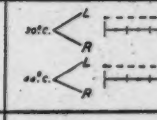
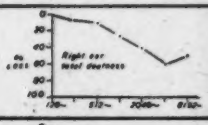
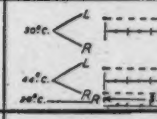
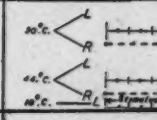
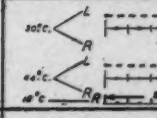
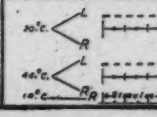
15	16			17	18
oric Tests	Summary of Results of Functional Tests			Treatment	Results
	Cochlear		Caloric		
	Left	Right			
	D. (Sl.)	D. (Sl.)	Left canal paresis. Moderate	Phenobarbital	Vertigo much diminished
	N.	N.	,,	Phenobarbital	Vertigo diminished
	D. (Sl.)	D. (S.)	,,	Phenobarbital	Vertigo slightly diminished
	D. (S.)	N.	,,	Left labyrinthectomy	Vertigo abolished Tinnitus diminished
	D. (S.)	N.	,,	Left labyrinthectomy	Vertigo diminished Tinnitus unchanged
	N.	N.	Right canal paresis. Moderate	Phenobarbital	Vertigo diminished
	N.	N.	,,	Phenobarbital	No note
	D. (Sl.)	D. (M.)	,,	Right labyrinthectomy	Vertigo much diminished Tinnitus unchanged
	N.	N.	Left canal paresis. Severe	Phenobarbital	No note
	D. (M.)	N.	,,	No note	No note

CLASS II. Canal paresis alone *(continued)*.

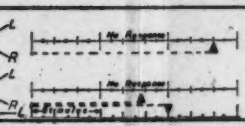
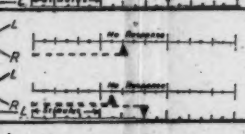
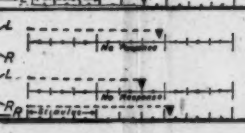
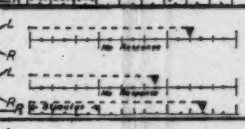
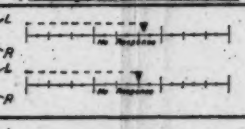
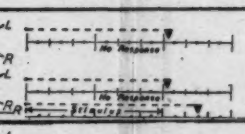
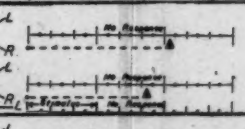
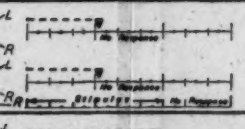
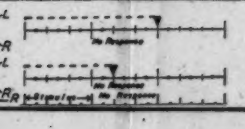
1	2	3	4		5	6	7	8	9		10		11		12		13		
Case No.	Sex	Age	Tinnitus (T) Deafness (D) Duration in years		Vertigo Duration in years	Nausea (N) Vomiting (V) Headache (H) with Vertigo	Mode of Onset of Vertigo	Clinical Evidence of Oro-nasal Sepsis	Tympanic Membranes		Whisper N. 30 ft.		Watch N. 18 in.		Rinné 512~		Weber 512~		Au
			Left	Right					Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	
GROUP 2 Severe *(continued)*																			
L.N. 21	♀	50	T. 2 $\frac{9}{12}$ D.2 $\frac{6}{12}$	Nil	3	N. V.	Slow. Preceded by nausea	Nil. No X-rays	N.	N.	5 ft.	>20 ft.	N.H.	18 in.	false −	+		→	
E.S. 22	♀	46	T.20 D.20	T. 20 D. 20	$\frac{5}{12}$	N. V.	Rapid. No aura	Nil. No X-rays	N.	N.	4 ft.	D.(C)			−	false −	←		
H.B. 23	♀	42	T.4	T.4 D. $\frac{3}{12}$	2	H.	Rapid. No aura	Nil. X-rays negative	N.	N.	20 ft.	15 ft.	2 in.	2 in.	+	+	← →		
I.P. 24	♀	41	T. $\frac{6}{12}$ D. $\frac{7}{12}$	Nil	$\frac{6}{12}$	N. V.	Slow. Aura of general weakness	Nil. X-rays negative	N.	N.	5 ft.	>20 ft.	N.H.	15 in.	false −	+		→	
B.C. 25	♂	56	T.5 D.5	Nil	1	V.	Rapid. Aura of pressure in head	Nil. X-rays negative	N.	N.	5 ft.	>20 ft.			+	+		→	
L.B. 26	♀	42	Nil	D. 28	1	H.	Rapid. No aura	Nil. No X-rays	Chalk patches + +	Old healed posterior perf.	5 ft.	D.(C)	1 in.		+	false −	←		
E.L. 27	♀	40	Nil	T. 3½ D. 3½	4½	V.	Rapid. Preceded by tinnitus and deafness right ear	Nil. No X-rays	N.	N.	>20 ft.	20 ft.	12 in.	3 in.	+	±	←		
T.M. 28	♂	56	T. $\frac{3}{12}$	T. $\frac{3}{12}$	$\frac{1}{12}$	Nil	Slow. No aura	Suppuration right antrum	N.	N.	15 ft.	7 ft.	N.H.	N.H.	+	+		→	
E.B. 29	♀	55	T. $\frac{3}{12}$ D. $\frac{3}{12}$	T. $\frac{3}{12}$ D. $\frac{3}{12}$	$\frac{3}{12}$	N. V. H.	Rapid. No aura	Nil. No X-rays	N.	N.	10 ft.	D. (C.)	N.H.	N.H.	+	false −	←		
J.P. 30	♂	46	Nil	D.3	4	N. V.	Slow. No aura	Nil. X-rays negative	N.	N.	>20 ft.	4 in.	At meatus	N.H.	+	false −	← →		

9		10		11		12		13		14	15
Tympanic Membranes		Whisper N. 30 ft.		Watch N. 18 in.		Rinné 512~		Weber 512~		Audiogram	Caloric Tes
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right		
N.	N.	5 ft.	>20 ft.	N.H.	8 in.	false −	+				
N.	N.	4 ft.	D.(C)			−	false −				
N.	N.	20 ft.	15 ft.	2 in.	2 in.	+	+				
N.	N,	5 ft.	>20 ft.	N.H.	15 in.	false −	+				
N.	N.	5 ft.	>20 ft.			+	+				
Chalk ?tches +	Old healed poster-ior perf.	5 ft.	D.(C)	1 in.		+	false −				
N.	N.	>20 ft.	20 ft.	12 in.	3 in.	+	±				
N.	N.	15 ft.	7 ft.	N.H.	N.H.	+	+				
N.	N.	10 ft.	D. (C.)	N.H.	N.H.	+	false −				
N.	N.	>20 ft.	4 in.	At meatus	N.H.	+	false −				

15	16			17	18
aloric Tests	Summary of Results of Functional Tests			Treatment	Results
	Cochlear		Caloric		
	Left	Right			
	D. (M.)	N.	Left canal paresis. Severe	Phenobarbital	Vertigo diminished
	D. (M.)	D. (C.)	,,	Phenobarbital	Vertigo diminished
	D. (Sl.)	D. (Sl.)	,,	Phenobarbital	Vertigo much diminished
	D. (M.)	N.	,,	Phenobarbital	Vertigo diminished
	D. (M.)	N.	,,	Left labyrinthectomy	Vertigo much diminished Tinnitus intermittent
	D. (M.)	D. (C.)	Right canal parésis. Severe	Phenobarbital	Vertigo unchanged
	N.	D. (Sl.)	,,	Phenobarbital	No note
	D. (Sl.)	D. (M.)	,,	Antral lavage. Phenobarbital	No note
	D. (M.)	D. (C.)	,,	Phenobarbital	Vertigo diminished
	N.	D. (V.S.)	,,	No note	No note

CLASS II. Canal paresis alone *(continued)*.

	1	2	3	4		5	6	7	8	9		10		11		12		13		
	Case No.	Sex	Age	Tinnitus (T) Deafness (D) Duration in years		Vertigo. Duration in years	Nausea (N) Vomiting (V) Headache (H) with Vertigo	Mode of Onset of Vertigo	Clinical Evidence of Oro-nasal Sepsis	Tympanic Membranes		Whisper Normal (N.) 20 ft.		Watch Normal (N.) 18 in.		Rinné 512~		Weber 512~		
				Left	Right					Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	
GROUP 3 Very severe	A.D. 31	♂	62	T. 9½ D. 9½	Nil	10	N. H.	Rapid. No aura	Nil. No X-rays	N.	N.	At Meatus	14 ft.	N.H.	N.H.	false —	+		→	
	D.S. 32	♀	40	T. 3	Nil	3	N. V.	Slow. No aura	Nil. X-rays negative	N.	N.	>20 ft.	>20 ft.	12 in.	18 in.	+	+	←	→	
	F.D. 33	♂	25	Nil	T.1½ D.3	1½	N. H.	Rapid. Preceded by headache	Nil. X-rays negative	N.	N.	>20 ft.	12 ft.	6 in.	N.H.	+	false —	←		
	A.F. 34	♂	33	Nil	D.4	$\frac{5}{12}$	V.	Slow. No aura	Tonsils infected. X-rays negative	N.	N.	>20 ft.	2 ft.	18 in.	4 in.	+	false —	←		
	C.F. 35	♂	47	Nil	T.10 D.10	4	N. V.	Slow. Preceded by increase of tinnitus and deafness	Nil. X-rays negative	N.	N.	20 ft.	6 in.	4 in.	N.H.	+	+	←		
	W.S. 36	♂	53	Nil	T.12 D.2	2	No note	Slow. No aura	Nil. X-rays negative	N.	N.	4 ft.	D. (C.)			+	false —	←		
GROUP 4 Complete	S.B. 37	♂	31	T.5. D.5.	T.5 D.5	3½	N. V. H.	Slow. Preceded by headache and increase of deafness and tinnitus	Nil. X-rays negative	N.	N.	3 ft.	3 in.			+	+			
	W.H. 38	♂	48	Nil	T.3 D.3	3	N. V. H.	Slow. Preceded by tinnitus in right ear	Nil. No X-rays	N.	N.	10 ft.	2 ft.	2 in.	N.H.	+	false —		→	
	G.S. 39	♂	28	T.1	T.+D. many years	1	N. V.	Rapid. No aura	Nil. No X-rays	N.	N.	20 ft.	2 ft.	N.H.	N.H.	+	+	←	→	

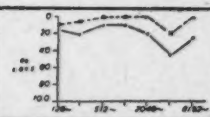
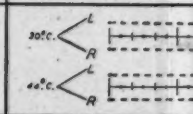
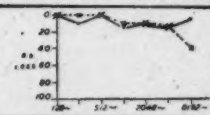
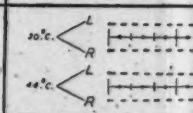
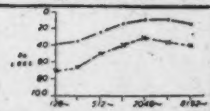
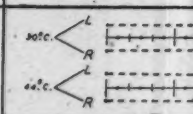
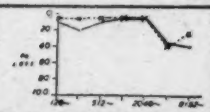
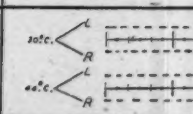
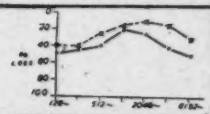
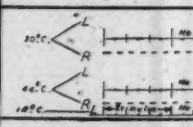
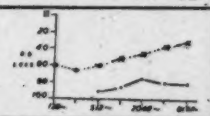
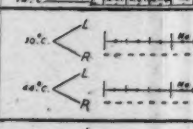
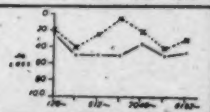
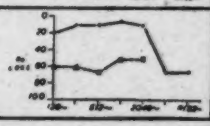
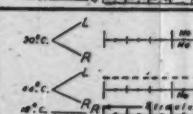
	9		10		11		12		13		14	
	Tympanic Membranes		Whisper Normal (N.) 20 ft.		Watch Normal (N.) 18 in.		Rinné 512~		Weber 512~		Audiogram	Caloric
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right		
	N.	N.	At Meatus	14 ft.	N.H.	N.H.	false −	+		→		
	N.	N.	>20 ft.	>20 ft.	12 in.	18 in.	+	+	←	→		
e	N.	N.	>20 ft.	12 ft.	6 in.	N.H.	+	false −	←			
e	N.	N.	>20 ft.	2 ft.	18 in.	4 in.	+	false −	←			
e	N.	N.	20 ft.	6 in.	4 in.	N.H.	+	+	←			
e	N.	N.	4 ft.	D. (C.)			+	false −	←			
e	N.	N.	3 ft.	3 in.			+	+				
	N.	N.	10 ft.	2 ft.	2 in.	N.H.	+	false −		→		
	N.	N.	20 ft.	2 ft.	N.H.	N.H.	+	+	←	→		

15	16			17	18
Caloric Tests	Summary of Results of Functional Tests			Treatment	Results
	Cochlear		Caloric		
	Left	Right			
	D. (V.S.)	D. (Sl.)	Left canal paresis very severe	Phenobarbital and bromide	Vertigo unchanged
	N.	N.	,,	Phenobarbital Salt restriction, etc., as in-patient	Vertigo increased
	N.	D. (Sl.)	Right canal paresis very severe.	Decompression of saccus endolymphaticus	Vertigo abolished
	N.	D. (S.)	,,	Right labyrinthectomy	Vertigo much diminished
	D. (Sl.)	D. (S.)	,,	Right labyrinthectomy	Vertigo abolished
	D. (M.)	D. (C.)	,,	Right labyrinthectomy	Vertigo abolished Tinnitus less
	D (M.)	D. (S.)	Left canal paresis complete	Phenobarbital	Vertigo diminished
	D. (M.)	D. (S.)	Right canal paresis complete	No note	No note
	D. (Sl.)	D. (S.)	,,	No note	No note

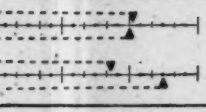
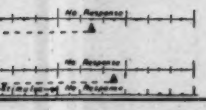
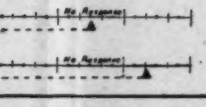
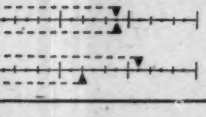
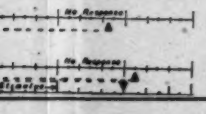
CLASS III. Directional preponderance and canal paresis in combination. 8 cases. Group 1—No d

	1	2	3	4		5	6	7	8	9		10		11		12		13	
	Case No.	Sex	Age	Tinnitus (T) Deafness (D) Duration in years		Vertigo. Duration in years	Nausea (N) Vomiting (V) Headache (H) with Vertigo	Mode of Onset of Vertigo	Clinical Evidence of Oro-nasal Sepsis	Tympanic Membranes		Whisper N. 30 ft.		Watch N. 18 in		Rinné 512~		Weber 512~	
				Left	Right					Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
GROUP 1 No dominant element	B.B. 40	♂	29	T. $1\frac{1}{2}$	T.1	1	N. V. H.	Rapid. Preceded by increase of tinnitus	Nil. X-rays negative	N.	N.	> 20 ft.	> 20 ft.	12 in.	18 in.	+	+		
	E.J. 41	♀	35	T. + D. recent	Nil	$\frac{8}{12}$	N. V. H.	Slow. No aura	Nil. X-rays negative	N.	N.	15 ft.	15 ft.	8 in.	12 in.	+	+		
	A.A. 42	♀	49	Nil	T.6 D.5	6	N. V. H.	Rapid. No aura	Drainage of Rt. antrum 6 yrs. ago. X-rays now neg.	N.	N.	> 20 ft.	15 ft.	3 in.	1 in.	+	+		
	F.N. 43	♂	58	Nil	Nil	$\frac{2}{52}$	N. V.	Rapid. No aura	Nil. X-rays negative	N.	N.	> 20 ft.	> 20 ft.	9 in.	9 in.	+	+		
GROUP 2 Canal Paresis dominant	L.J. 44	♀	35	T. $\frac{11}{12}$	Nil	1	N. V. H.	Slow. Preceded by nausea	Nil. X-rays negative	N.	N.	> 20 ft.	> 20 ft.	1 in.	9 in.	+	+		
	J.R. 45	♂	20	T.4 D.4	T.$3\frac{1}{2}$ D.$3\frac{1}{2}$	4	Nil	Slow. Preceded by increase of tinnitus and deafness	Acute infection left antrum	N.	N.	D.(C.)	10 ft.	N.H.	4 in.	false −	+		
	A.T. 46	♂	43	T. $\frac{9}{12}$ D. $\frac{9}{12}$	Nil	$1\frac{1}{2}$	V.	Rapid. No aura	Nil. No X-rays	N.	N.	8 ft.	20 ft.	N.H.	3 in.	false −	+		
	P.D. 47	♂	58	Nil	T.11 D.2	10	N. V.	Rapid. Preceded by increase of tinnitus	Nil. X-rays negative	N.	N.	12 ft.	D.(C.)	N.H.		+	false		

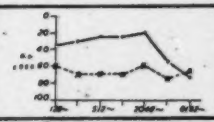
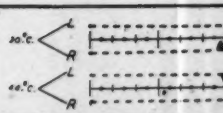
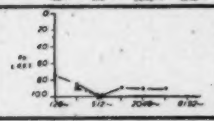
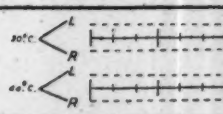
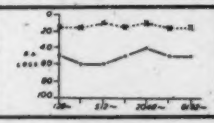
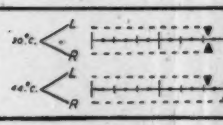
combination. 8 cases. Group 1—No dominant element, 4 cases.

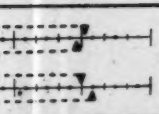
9		10		11		12		13		14	15
Tympanic Membranes		Whisper N. 30 ft.		Watch N. 18 in		Rinné 512~		Weber 512~		Audiogram	Caloric Tes
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right		
N.	N.	> 20 ft.	>20 ft.	12 in.	18 in.	+	+				
N.	N.	15 ft.	15 ft.	8 in.	12 in.	+	+				
N.	N.	> 20 ft.	15 ft.	3 in.	1 in.	+	+				
N.	N.	> 20 ft.	>20 ft.	9 in.	9 in.	+	+				
N.	N.	> 20 ft.	>20 ft.	1 in.	9 in.	+	+				
N.	N.	D.(C.)	10 ft.	N.H.	4 in.	false −	+				
N.	N.	8 ft.	20 ft.	N.H.	3 in.	false −	+				
N.	N.	12 ft.	D.(C.)	N.H.		+	false				

es. Group 2—Canal paresis dominant, 4 cases.

15	16			17	18
aloric Tests	Summary of Results of Functional Tests			Treatment	Results
	Cochlear		Caloric		
	Left	Right			
	N.	N.	Left canal paresis with directional preponderance to right	Phenobarbital	Vertigo diminished
	D. (Sl.)	D. (Sl.)	,,	No note	No note
	N.	D. (Sl.)	Right canal paresis with directional preponderance to left	Phenobarbital	Vertigo much diminished
	N.	N.	,,	Phenobarbital and pilocarpine	Vertigo diminished
	N.	N.	Left canal paresis with directional preponderance to right	Phenobarbital	Vertigo increased
	D. (C.)	D. (M.)	,,	Antral lavage. Phenobarbital	Vertigo deafness diminished
	D. (M.)	D. (Sl.)	,,	Phenobarbital	No note
	D. (Sl.)	D. (C.)	Right canal paresis with directional preponderance to left	No note	No note

CLASS IV. Normal. 3 cases.

1	2	3	4		5	6	7	8	9		10		11		12		13		
Case No.	Sex	Age	Tinnitus (T) Deafness (D) Duration in years		Vertigo. Duration in years	Nausea (N) Vomiting (V) Headache (H) with Vertigo	Mode of Onset of Vertigo	Clinical Evidence of Oro-nasal Sepsis	Tympanic Membranes		Whisper N. 30 ft.		Watch N. 18 in.		Rinné 512~		Weber 512~		
			Left	Right					Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	
C.H. 48	♂	54	Nil	T.25 D.25	1	N. V. H.	Rapid. No aura	Antral suppuration left and right	N.	Scarring	15 ft.	At meatus	N.H.	N.H.	+	+	←		
A.P. 49	♂	47	T.$\frac{5}{512}$	D.6	4	H.	Slow. No aura	Nil. No X-rays	N.	N.	9 in.	At meatus	N.H.	N.H.	±	±	←		
A.T. 50	♂	40	D.4	Nil	5	N. V.	Rapid. No aura	Nil X-rays negative	Scarring	N.	8 ft.	15 ft.	1 in.	6 in.	+	+	← →		

9		10		11		12		13		14	15
Tympanic Membranes		Whisper N. 30 ft.		Watch N. 18 in.		Rinné 512~		Weber 512~		Audiogram	Caloric Tests
ft	Right	Left	Right	Left	Right	Left	Right	Left	Right		
.	Scarring	15 ft.	At meatus	N.H.	N.H.	+	+	←			
.	N.	9 in.	At meatus	N.H.	N.H.	±	±	←			
ring	N.	8 ft.	15 ft.	1 in.	6 in.	+	+	←	→		

	16		17	18
ests	Summary of Results of Functional Tests		Treatment	Results
	Cochlear	Caloric		
	Left / Right			
	D. (Sl.) / D. (V.S.)	Normal	Drainage of antra. Phenobarbital	Vertigo much diminished
	D. (S.) / D. (V.S.)	Normal	No note	No note
	D. (M.) / D. (Sl.)	Normal	Drainage of saccus endolymphaticus	Vertigo much diminished

CHRONIC THYROTOXIC MYOPATHY.[1]

A Report of Three Cases with a Review of Previously Reported Cases.

BY DONALD McEACHERN AND W. D. ROSS.

In view of the hopeless prognosis attaching to progressive muscular atrophy in our present stage of knowledge it is important to distinguish a group of cases which resemble this disorder clinically but are amenable to treatment. Such a group is comprised of cases with muscular atrophy in association with hidden thyrotoxicosis. Recovery occurs following thyroidectomy.

Brain (1938) has presented a classification of muscular disorders associated with hyperthyroidism. We are concerned at present with the group designated as chronic thyrotoxic myopathy. A careful survey of the literature to the end of 1940 has revealed ten well described cases which belong in this group. Several cases published at the beginning of the century might also belong in this category but the reports lack completeness without basal metabolism determinations and thyroidectomies (Bathurst, 1895; Miesowicz, 1904; and Sattler, 1909). Some cases belonging in the group under consideration may have been reported as cases of myasthenia gravis with hyperthyroidism. In at least two instances, Rennie's case (1919) and Sterling's case (1930), the same case seems to have been taken as myasthenia gravis by one author and chronic thyrotoxic myopathy by another (Brain, 1938; Ayer, Means and Lerman, 1935; Rennie, 1908 and 1919; and Cohen and King, 1932). One recent report presents certain confusing features which throw doubt on its inclusion in this group (Bernal, 1939).

We present an account of three cases and a table summarizing the chief features of the previously reported cases and of those observed by us (Table I).

Case Reports.

Case 1.—H. A. E., aged 45, male physician, admitted to Montreal Neurological Institute October 6, 1937, No. 2939. Complaining of generalized weakness, muscular fatigability and loss of 27 lb. weight in preceding eight months. Excessive perspiration, nervousness and emotional instability had been noted for three months and generalized muscular twitching for two months.

[1] From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute, Montreal.

Examination.—Resting pulse-rate 100 to 120, blood-pressure 136 to 154 systolic, 100 to 110 diastolic. Marked apprehensiveness and emotional lability, skin warm and moist, no exophthalmos nor hyperthyroid eye signs, thyroid not enlarged. There was rapid, coarse tremor of the outstretched hands. Generalized muscular wasting was evident, most marked in regions of trunk, shoulder girdle and proximal parts of limbs. Small muscles of hands were also affected. Limbs on right side somewhat more wasted than on left. Intense generalized muscular fasciculation was present. Abdominal muscles were very weak and there was considerable respiratory difficulty due to weakness of lower intercostal muscles and poor excursion of right diaphragm (fluoroscopic). There was marked myasthenia and the limb muscles fatigued after a few strokes against resistance. Severe cramps occurred in muscles of upper and lower limbs after sleep or a period of rest, but none occurred after the limbs had been used for a few minutes.

There were no symptoms or signs suggesting involvement of muscles innervated by the cranial nerves. Deep reflexes in upper and lower limbs were equal and slightly hyperactive on the two sides; plantar responses were flexor. There was no sensory defect. B.M.R. on two separate occasions +28% and +27% respectively. C.S.F.: Cells 0, proteins 23 mgm.%, Pandy negative. Gastric analysis: Fasting 0, after alcohol 18. Complete hæmogram: Normal. Chest X-ray: Negative save for paresis of right diaphragm. Wassermann in blood and cerebrospinal fluid negative. Serum: Na 331 mgm.%, K 16·3 mgm.%, Ca 10·2 mgm.%, P 4·02 mgm.%. Myogram (Pritchard, 1933): Myasthenic defect, improvement after 0·4 mgm. prostigmine. Novocain block of peroneal nerve on two occasions (Russel, Odom and McEachern, 1938): Fibrillation continued in anterior tibial muscles, indicating a peripheral mechanism.

Diagnosis.—Progressive muscular atrophy. The patient returned home receiving high vitamin therapy, calcium and adrenal cortex extract. Three weeks later he died suddenly of respiratory paralysis. No autopsy was obtained. In retrospect this is a case of chronic thyrotoxic myopathy.

Case 2.—J. S., male, aged 55, admitted to Royal Victoria Hospital June 19, 1939, No. 82388 (Service Dr. E. H. Mason). Complaints: Increasing weakness, fatigability and dizziness for two months with loss of 30 lb. weight and excessive thirst, nycturia and headaches for one month. Glycosuria had been observed prior to admission and patient was admitted with diagnosis of diabetes mellitus.

Examination in hospital failed to confirm diagnosis of diabetes. Patient was apprehensive, emotionally unstable. Skin warm and moist, slight prominence of eyeballs, marked fine tremor of hands. Resting pulse-rate 90 to 110, B.P. 128/68. No thyroid enlargement. There was generalized muscular wasting, most evident in small muscles of hands and feet. Rapid muscular fasciculation was present everywhere. Myasthenia was marked, the limbs tiring quickly against resistance. Weakness was so great that the patient could not get out of bed or raise the legs against slight resistance. There was no weakness of muscles innervated by the cranial nerves. Tendon reflexes were hyperactive but equal on the two sides, plantars flexor. There was no defect of sensation. Myogram taken from the fifth digit after electrical stimulation of the ulnar nerve showed the myasthenic defect (Russel, Odom and McEachern, 1938). The myogram returned toward normal (fig. 1) after intramuscular injection of 1·0 mgm. prostigmine and there was great improvement in muscle power, the patient being able to get out of bed and walk for several hours.

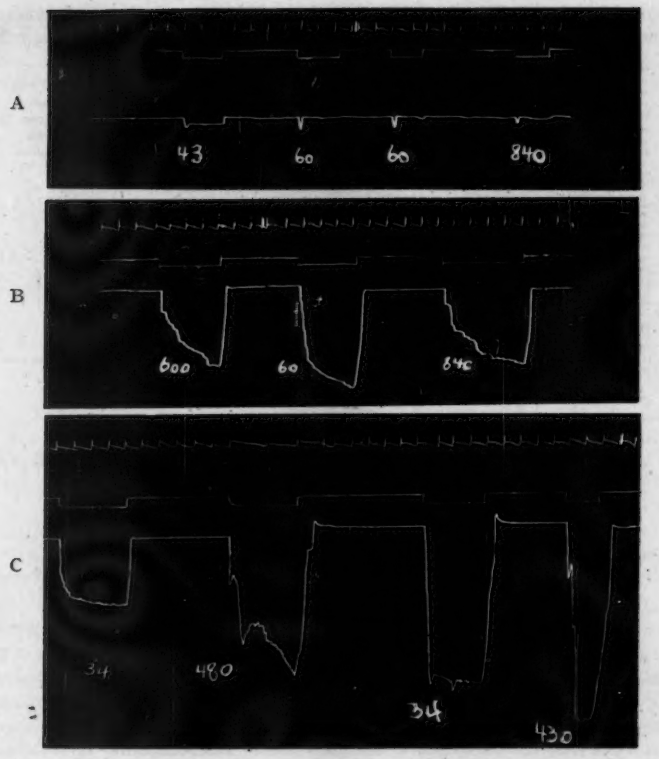


FIG. 1.—Myograms from Case 2. A, before operation. B, before operation but after injection of prostigmine. C, after operation, no prostigmine. In each instance from above downward: Time signal in seconds, stimulation signal, myogram. Numbers indicate number of stimuli per second. Irregularities in curves are due to muscular fasciculation.

Laboratory information relating to the state of hyperthyroidism is pictured in fig. 2. Other data: Serum Na 335 mgm.%, K 17·9 mgm.%, Ca 11·7 mgm.%, P 4·3 mgm.%. Glucose tolerance test: High prolonged curve. Wassermann in blood and C.S.F. negative. Hæmogram not abnormal. Chest X-ray negative; no evidence substernal thyroid.

Diagnosis: Chronic thyrotoxic myopathy.

August 3, 1939: The administration of Lugol's solution was begun (minims v, t.i.d.). August 8: Myogram normal without prostigmine. August 26: Subtotal thyroidectomy; thyroid not enlarged. Pathological report: "Diffuse glandular goitre. Sections on a whole resemble Graves' disease more than adenoma." Myogram October 15, 1939, normal (fig. 1).

The patient made slow recovery thereafter, some evidences of hyperthyroidism and muscular fasciculation remaining for many months. Onset of peptic ulcer

complicated recovery. When examined on June 30, 1941, two years after admission to hospital, the patient was well and doing heavy work as a junk collector. Muscle

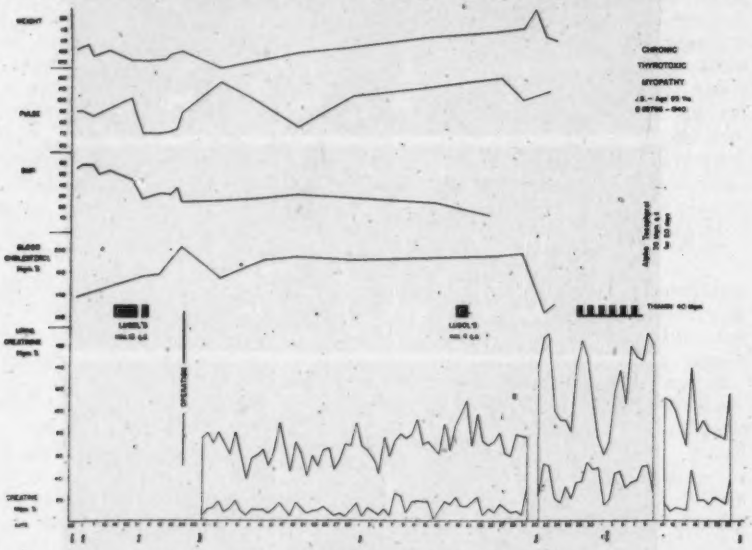


FIG. 2.—Clinical and chemical course of Case 2.

power, nutrition and endurance were normal; there was no fasciculation. Tendon reflexes normal, plantars flexor. Weight 120 lb., a gain of 30 lb. Pulse-rate 76. B.M.R. +17. There was, however, moderate exophthalmos, upward conjugate movement of the eyes was limited to 10° above the horizontal and there was moderate external rectus weakness on each side. Exophthalmic ophthalmoplegia had apparently developed. No other weakness of muscles innervated by the cranial nerves was present.

Case 3.—C. C., male, aged 46, admitted to Montreal Neurological Institute October 17, 1940, No. 6341. Complaints: Generalized weakness and fatigability, nervousness, tremor of hands and headaches for six months. Loss of 17 lb. weight in four months. Examination showed a very apprehensive man. Resting pulse-rate 90 to 110, B.P. 136/78. Skin moist but not warm, no exophthalmos or hyperthyroid eye signs. Marked tremor of hands which interfered with handwriting. Coarse, rapid fascicular twitchings were generalized, most marked in buttocks and lower limbs, left greater than right. No muscular wasting. There was no sensory defect nor evidence of involvement of muscles innervated by the cranial nerves. Tendon reflexes were exaggerated in upper and lower limbs but equal on the two sides. Plantars flexor. Thyroid not palpably enlarged.

Laboratory information relating to the state of hyperthyroidism is presented in fig. 3. Other data: Chest X-ray, no evidence substernal thyroid or enlarged thymus. Glucose tolerance curve normal. Serum: K 18·9 mgm.%, Na 334 mgm.%, Ca 10·9 mgm.%, P 2·12 mgm.%. Blood Wassermann negative.

Diagnosis.—Chronic thyrotoxic myopathy. A diagnosis of anxiety neurosis had been long entertained by a number of observers because of the clinical picture and because of patient's known psychological difficulties.

Therapy with Lugol's solution ♏ vii, t.i.d. was begun on October 26 and a good remission was obtained. Subtotal thyroidectomy on November 2 revealed a firm moderately enlarged gland with a hard nodule at left upper pole. Pathological report: "Diffuse glandular goitre, Graves' disease."

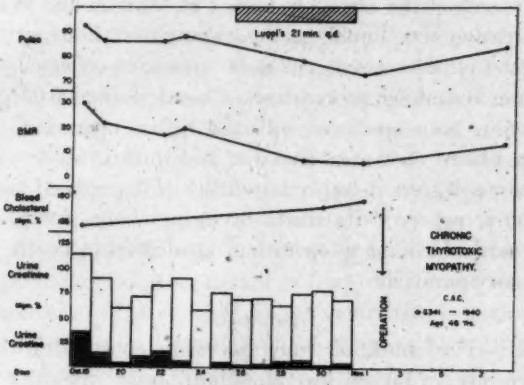


FIG. 3.—Clinical and chemical course of Case 3.

On November 14 examination showed that most of the signs and symptoms had vanished. Tremor had disappeared from right hand, still slightly present in left hand. Fasciculation was still present, especially in left lower limb, but was slower and less prominent than before operation. May 28, 1941, six months after operation, the patient reported: Working full time, gain of 20 lb. in weight, tremor of hands absent, handwriting normal, muscular twitchings "about disappeared." He still suffered from headaches.

CLINICAL PICTURE.

The chief features of the thirteen cases presented in Table I are as follows: Sex incidence predominantly in males (11 to 2). Age incidence 24 to 62 years, with twelve cases between 39 and 62 years. The main symptoms were weakness and loss of weight with muscular wasting. Symptoms suggestive of hyperthyroidism such as nervousness and excessive perspiration were often present but not so prominent as the weakness and fatigability. Onset was gradual, usually leading to hospital admission within a year. Findings on examination included elevated pulse-rate and often increased pulse-pressure. There was seldom any exophthalmos and only slight, if any, palpable enlargement of the thyroid gland. Tremor of the outstretched hands was prominent and general muscular wasting with fasciculation was most marked in shoulder and pelvic girdles and less so peripherally in the small muscles of the hands and feet. B.M.R. was elevated from +14 to +68 per cent. in twelve of the cases and to +100 per cent. in one case. The latter case showed the characteristic muscular

wasting but differed from the other cases in age and in severity of hyperthyroid signs. Blood cholesterol, when studied, was low or normal. Glucose tolerance was normal or reduced. Creatinuria was present, and glycosuria in some of the cases. In Case 1 of Morgan and Williams (1940) 0·14 grm. creatine was found in the twenty-four hour urine specimen, two days after thyroidectomy. A similar specimen collected three months after operation contained no creatine. Case 2 showed 0·04 grm. creatine in a twenty-four hour specimen collected before operation. Two of our patients were placed on a meat-free diet and showed moderate creatinuria as long as some degree of hyperthyroidism still persisted (figs. 2 and 3). Thyroidectomy, when performed, brought about complete recovery. Three cases not submitted to operation terminated in death, two of these from respiratory paralysis.

Discussion.

Diagnosis.—The condition may be easily confused with progressive muscular atrophy. Marked loss of weight, brisk muscular fasciculation and wasting, generalized weakness and fatigability dominate the picture. Signs and symptoms of hyperthyroidism are present but seldom full-blown and are apt to be attributed to the general discomfort and apprehension of the patient.

Unlike progressive muscular atrophy, the muscles of the shoulder and hip girdles and the proximal muscles of the limbs are apt to be first and most affected, although the small muscles of hands and feet often suffer. The degree of weakness and fatigability may be greatly out of proportion to the amount of muscular wasting, whereas in progressive muscular atrophy they tend to parallel one another. Muscular fasciculation is often very active and is apt to involve large sheets of muscles and be more flash-like than the fasciculation of progressive muscular atrophy. In two of our cases it was so coarse in the lower limbs that it caused marked tremulousness and " giving away " of the legs, to which the patients attributed their tendency to fall when walking. Severe muscular cramps are apt to occur during the night or on first using the limbs in the morning. This tendency, also seen in some cases of progressive muscular atrophy, wears off after a short period of muscular activity. In a few cases fasciculation is very slight or absent and the picture may then suggest muscular dystrophy.

Tendon reflexes are normal or symmetrically hyperactive. Hyperactive tendon-jerks should not be construed as necessarily a sign of pyramidal tract involvement since they are usually but a part of the general increase

in muscular excitability. There are no signs of corticobulbar or corticospinal tract involvement such as we see in amyotrophic lateral sclerosis, e.g. spasticity, absent abdominal reflexes or extensor plantar responses. One side of the body may be affected earlier and more severely than the other, as in our Cases 1 and 3. This may seem to argue against a metabolic cause but is answered by the fact that the muscles recover equally when the cause is removed. Furthermore, one-sided predominance is well known to occur in certain other metabolic disorders affecting the neural or neuromuscular systems, e.g. myasthenia gravis, familial periodic paralysis (Pudenz, McIntosh and McEachern, 1938), transient hemiplegia due to hypoglycemia, vasocontriction due to adrenalin-forming tumor.

Anxiety, emotional lability, loss of weight, sweating, tremor of the hands, heat intolerance and moderate tachycardia are the main evidences of hyperthyroidism. The marked apprehensiveness is noteworthy since it is often absent even in critical cases of progressive muscular atrophy. In several cases temporary glycosuria has been marked and in our Case 2 led to an early diagnosis of diabetes.

Remission of signs and symptoms during iodine therapy is the rule, although in one case no improvement occurred whilst cure later resulted from thyroidectomy. At operation the thyroid gland is found to be not enlarged or larger than suspected. The microscopic picture is one of hyperplastic goitre.

After operation the muscular weakness and other signs of hyperthyroidism improve rapidly, but muscular atrophy and fasciculation may take weeks or months to disappear.

Myasthenia.—Rapid fatigability of trunk and limb muscles is a striking feature. In our Case 1, movements of the limbs against resistance were powerfully initiated but weakened greatly after five or ten repetitions. Myograms were feeble but strengthened after 0·4 mgm. prostigmine intramuscularly. In Case 2 the extended legs could not be raised from the bed, and standing was impossible. After i.m. injection of 1·0 mgm. prostigmine Wedensky inhibition disappeared from the myogram and the patient was able to walk about the ward for several hours. In Morgan and Williams' first case (1940) prostigmine gave subjective improvement not shown by ergogram.

Our patients had myasthenia of trunk and limb muscles but not myasthenia gravis. They showed no weakness or fatigability of muscles innervated by the cranial nerves. It would be interesting to know why the phenomenon of fatigability elects two such different territories in the

two conditions. That the two conditions may not be so far apart is indicated by the response to prostigmine. Our patient 2 developed deficiency of eyeball movements (probably due to exophthalmic ophthalmoplegia) long after thyroidectomy, at a time when the thyrotoxic myopathy had cleared. In Starling's case (1938) exophthalmic ophthalmoplegia was present along with thyrotoxic myopathy. The mechanism of exophthalmic ophthalmoplegia is probably quite different, however, from that of myasthenia gravis (see *Brain*, 1938).

Fasciculation.—Clinically it is difficult to distinguish various types of muscular fibrillation and fasciculation as Denny-Brown and Pennybacker (1938) have so ably done by electro-myographic methods. The fine, almost invisible fibrillations described by Langley and Kato (1914-15) in animals, as a result of simple denervation of the muscle fibre, is seldom if ever observed through the human integument. In chronic thyrotoxic myopathy the involuntary twitchings are coarse and involve fascicles or fairly large sheets of muscle. They are indistinguishable from the coarse fasciculation sometimes seen in amyotrophic lateral sclerosis, although we have the impression that they are apt to be grosser and cause more involuntary movement of extended digits or even of the limbs. Marked tremulousness of the legs with a tendency to fall, and inco-ordination of the arms with a tendency to drop things seemed to be associated with these contractions in our three patients.

It has been generally held that the fasciculation of amyotrophic lateral sclerosis and progressive muscular atrophy is due to abnormal discharges coming down the motor nerve fibres from degenerating anterior horn cells. It has been shown (Russel, Odom and McEachern, 1938), however, that such fasciculation persists following novocain block of the motor nerve, thus indicating a peripheral mechanism. The above procedure was carried out in Case 1 of the present series and fasciculation remained unchanged in the muscles temporarily deprived of their motor nerve supply.

Denervated skeletal muscle is known to become increasingly sensitive, after a period of about five days, to the chemical transmitter acetylcholine, and Denny-Brown and Pennybacker (1938) have suggested this explanation for fasciculation in amyotrophic lateral sclerosis. No degeneration of pyramidal tracts or motor neurones occurs in chronic thyrotoxic myopathy, however, and recovery is complete following thyroidectomy. Fasciculation would therefore have to be ascribed to one or other of the following causes:

(1) Increased sensitivity of end-plates or muscle fibres due to metabolic changes resulting from hyperthyroidism.

(2) Increase of the Cholinergic transmitting mechanism of skeletal muscle due to: (*a*) Increased concentration of acetylcholine at the end-plates; (*b*) diminished concentration of cholinesterase.

The last explanation would duplicate conditions in the animal or human subject following large doses of prostigmine with atropine. Under such circumstances brisk generalized fasciculation occurs in the skeletal muscles whilst the visceral effects of the anticholinesterase drug are prevented by the atropine.

B.M.R. and Fasciculation.—Fasciculation is often so brisk in amyotrophic lateral sclerosis and progressive muscular atrophy that one wonders whether the muscular twitching alone might not raise the basal metabolism. We have studied 9 such cases with the following results: 7 cases, B.M.R. −7 per cent. to +12 per cent.; 2 cases, B.M.R. +17 per cent. and +24 per cent. respectively. Fasciculation cannot therefore be held responsible for the increased metabolism in cases of chronic thyrotoxic myopathy.

Summary and Conclusions.

Three cases of chronic thyrotoxic myopathy are described. Two patients recovered following thyroidectomy, one died undiagnosed. The information on ten cases previously reported in the literature is summarized.

The condition is usually seen in males past middle age and is characterized by progressive loss of weight and marked weakness, fatigability, wasting and coarse fasciculation of the skeletal muscles. There are no signs of pyramidal tract involvement. Muscular symptoms dominate the picture and the usual evidences of hyperthyroidism are in the background, although apprehensiveness, emotional lability and sweating are usually present. The basal metabolic rate is moderately increased. The thyroid gland is not palpably enlarged or only moderately so. Thyroidectomy is followed by complete recovery.

The distribution of muscular weakness and fatigability is not that of myasthenia gravis but may nevertheless respond temporarily to prostigmine. Fasciculation appears to be of peripheral origin, which suggests increased concentration of acetylcholine at the neuromuscular junctions, or a generally increased sensibility of muscle fibres to the chemical transmitter due to metabolic causes and not due to denervation. The increase of basal metabolism cannot be attributed to fasciculation since cases of amyotrophic lateral sclerosis showed no increase of metabolism despite equally brisk and widespread muscular twitching.

TABLE I.

Author	Age	Sex	Onset	Clinical symptoms	Pulse	B.P.	Exophthalmus	Thyroid enlarg.
Ayer, Means and Lerman (1935)	48	M.	7 weeks	Progressive weakness and wasting, marked muscular twitchings, dyspnœa. Weight loss 24 lb.	Rapid		+	+
Brain and Starling (1938)	43	M.	1 year grad. 8 days sudden	Diplopia worse later in the day. Weakness arms and legs. Weight loss 67½ lb.	80 to 85	135/75	R + + L +	Late
Brain, Darke and Hunt (1938)	60	M.	18 months	Weakness, muscular wasting, breathlessness, palpitations	110		+ + +	+ +
Parsons and Twort (1939)	50	M.	6 months	Dysphagia, increasing weakness arms and legs. Weight loss 26 lb.	90	145/100	+	0
MacKenzie (1940)	46	M.	8 months	Increasing weakness and fatigue. Weight loss 47 lb.		130/100	+	0
Morgan and Williams (1940)	52	M.	7 months	Weakness, numbness, tingling and muscle tremors, restless and irritable, palpitation. Loss 58 lb.	120	150/90	0	+ +
,,	39	M.	5 months	Weakness, diarrhœa, aching and twitching muscles, pronounced fatigue. Weight loss 52 lb.	86	130/75	0	+ + +
,,	62	M.	7 months	Weakness and shortness of breath. Restless and irritable. Loss 35 lb.	120	175/100	0	+
,,	60	F.	3 years	Cough and asthenia. Weight loss 30 lb.				+
del Castillo, de la Balze and Caul (1940)	24	F.	9 months	Nervousness, loss of weight, swelling in the neck, insomnia, hypomenorrhœa, diarrhœa.	130	152/70	+ +	+ + +
McEachern and Ross (1942) Case 1	45	M.	8 months	Weakness, fatigability, perspiration, nervousness and muscular twitchings. Weight loss 27 lb.	100 to 120	136/100	0	0
McEachern and Ross (1942) Case 2	55	M.	2 months	Weakness, fatigability and dizziness, thirst and nocturia. Loss 30 lb.	90 to 110	126/68	+	0
McEachern and Ross (1942) Case 3	46	M.	6 months	Weakness, fatigability, nervousness, headaches, tremor. Loss 17 lb.	90 to 110	136/78	0	0

Tremor	Fasciculations	Distribution of muscular wasting	B.M.R.	Cholesterol	Glucose tolerance	Urine creatine	Effect of operation
	"Generalized fibrillary twitchings"	Generalized more marked in face and temples	+ 58				Recovery
+		Proximal severely and distal slightly			Glycosuria		Recovery
+	"Occasional in tongue and legs"	Both limb girdles and hand except hypothenar	+ 44				Recovery
+	"Occasional in calves"	Generalized, mostly pelvic and shoulder girdles	+ 54				Recovery
+	"Infrequent fibrillary twitchings"	Back and shoulders, calves and hands	+ 33 + 45	186 mgm.	Reduced		Recovery
+	"Moderate fibrillary and fascicular"	Shoulder and pelvic girdles and hands	+ 47	83 mgm.	Slight glycosuria	0·14 grm. /24 hrs.	Recovery
+	"Coarse tremulousness of extremities"	Shoulder girdle and extremities	+ 46	156 mgm.	A.C. sugar 100 mgm.%	0·04 grm. /24 hrs.	Recovery
+	"Fibrillary and fascicular myœdema"	Legs, shoulder girdle and hands	+ 14 + 23	156 mgm.	A.C. sugar 70 mgm.%		Died of resp. paralysis before operation
	None	Forearm, thenar and hypothenar and interossei	+ 63				On road to recovery
+		Shoulder and hands and temporal muscles	+ 100		Blood sugar normal		Death without operation
+	Intense generalized	Generalized, most marked proximally	+ 28				Died of resp. paralysis
+	Rapid generalized	Generalized, most marked hands and feet	+ 58		High prolonged curve, Glycosuria	10—55 mgm.%	Recovery
+	Coarse, rapid, generalized	None	+ 29		Normal	6—37 mgm.%	Recovery

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PRIMARY DEGENERATION OF THE SPINAL CORD IN MONKEYS, A STUDY IN COMPARATIVE PATHOLOGY.

By A. E. HAMERTON.

In 1932 H. J. Sherer of the Institut Bunge, Antwerp, was the first to establish the existence of demyelinating disease of the spinal cord in macaque monkeys in the Zoological Gardens of that city. It was first recognized in the London Zoo in 1935.

During the last seven years I have studied the clinical and pathological findings in eleven cases of primary combined degeneration of the spinal cord occurring naturally in monkeys in the Zoological Gardens, London.

Specific Distribution.

The disease has been observed solely among Catarrhine (Old World) Monkeys of the African genera Cercopithecus, Erythrocebus, and in the Asiatic genus Macaca. I can find no record of any similar disease having occurred among Platyrrhine (New World) Monkeys or in any other Primate species except man.

Incidence of the Disease.

The "average strength" of the Monkey House population in the London Zoological Gardens in the seven-year period during which the disease has been studied is estimated at 100 monkeys, of which 80 were Old World species, 1·3 per cent. of which suffered from the disease during the specified period.

The species affected were:

3 Patas Monkeys (*Erythrocebus patas*).

4 Stair's Monkeys (*Cercopithecus albogularis*).

1 Green Monkey (*Cercopithecus sabæus*).

1 Mona Monkey (*Cercopithecus mona*).

1 White Nosed Monkey (*Cercopithecus nictitans*).

1 Toque Monkey (*Macaca sinica*).

Males and females are about equally susceptible to the disease. All the animals affected were fully mature, though not aged. The period of health in captivity before the onset of symptoms varied between one and half and eight and a half years, although most of the cases showed their first symptoms between the third and sixth year of captivity.

Duration of the Disease.

In untreated cases this was from one week to sixty-two weeks counting from the onset of initial symptoms to the final stage of complete flaccid paralysis and immobility of the hind limbs. At this stage the monkeys were killed by euthanasia for post-mortem examination.

History.—The eleven cases recorded had no history of any illness preceding the onset of paraplegia. In eight of them no gross pathological lesion or injury could be found associated with the degenerative changes in the spinal cord; the cord lesion itself was not obvious to the naked eye.

Of the three monkeys in which associated disease was found, one case showed diverticulitis with a small localized abscess in one of the colonic pouches. In a second monkey the disease of the central nervous system was complicated by a terminal serous leptomeningitis interna. A third monkey died suddenly from a traumatic ulcer of the colon and hepatic abscess, whilst under treatment for the primary nervous disease.

In three cases in which the stomach contents were analysed after a test meal, achlorhydria was found.

Repeated blood examinations were made in nine of the eleven monkeys, but abnormalities were found in two cases only. One of these showed a moderate degree of macrocytic anæmia and the other a lymphatic leukæmia associated with hyperplasia of the abdominal lymph glands.

Clinical Features.—Wild monkeys are difficult and aggressive patients, consequently clinical examinations cannot be carried out upon them as thoroughly as upon the human subject. Such clinical data as I have been able to collect from monkeys are therefore somewhat meagre. In all cases however the cardinal diagnostic signs are similar, namely, intention tremor of the hands, spastic paraplegia affecting the hind legs, a wobbling gait, a rapidly increasing ataxia with progressive loss of power and finally, a complete flaccid paralysis of the hind limbs and tail. The limb reflexes, at first increased, are lost in the final stages of the disease. Loss of sensation is a late symptom in most cases.

Vesical and rectal reflexes are usually unaffected. The essential clinical signs, which in all cases suffice to indicate a lesion of the antero-lateral

and postero-lateral columns of the spinal cord, may be summarized in tabular form:

Monkey.	*Period in Zoo Years.*	*Duration of Disease Weeks.*	*Cardinal Symptoms.*	*Test Meal.*	*Blood.*
Patas ..	2	3	Intention tremor of hands. Spastic paraplegia, ataxia progressing to flaccid palsy of hind limbs and tail.		
Patas ..	3½	23	do.	HCl—	Normal.
Patas ..	3½	5	do.		N
Patas ..	1½	20 Treated case.	do. (Functional cure 11 weeks)		N
Stair's ..	8½	10	do.		N
Stair's ..	6	1½ Rapid case.	do.	HCl—	N
Stair's ..	6	17 Treated case.	do. (Functional cure 2½ years. Then relapse)		
Stair's ..	5½	16	do.		Lymphatic. Leukæmia.
Green ..	3	1 Rapid case.	do. (Recurrent epileptiform fits)		Leucocytosis.
Toque ..	4½	5	do. (Spontaneous recovery. Relapse after 1 year)	HCl—	Pernicious anæmia.
White-nosed	2¾	5	do.		

Achlorhydria and macrocytic anæmia were associated in one case. In the remaining eight cases the pathological characteristics of this primary combined degeneration of the spinal cord were not associated with any complicating acute or chronic disease such as dysentery, tuberculosis, sepsis or other wasting maladies. The cerebrospinal fluid was normal in ten of the eleven cases examined. I will select some of the cases on the list for further consideration of the clinical details and the results of treatment.

A Toque Monkey (*Macaca sinica*) was first admitted to the Sanitarium in the Zoo, in April, 1936, for spastic paresis affecting the hind legs. It was kept under observation for five weeks without treatment. No injury could be detected; no other nervous symptoms developed. The animal made a spontaneous and complete recovery.

A year later it was readmitted with a recurrence of the nervous symptoms. There was now tremor of hands, complete flaccid paralysis of the right hind leg and a tonic spasm of the muscles of the left leg. The knee reflexes were increased; sensation was apparently lost in both legs, tests for ankle clonus and Babinski's reflex gave no response.

The blood picture at this stage was: Hæmoglobin 48 per cent., colour index 0·63 per cent., R.B.C. 3,800,000, W.B.C. 21,000, polymorphonuclear corpuscles in excess. Many of the R.B.C. were colourless, malformed, oversized or undersized, an occasional nucleated red cell was present and polychromatophilia was evident. When compared with records of normal monkey (Macaca) blood, the blood picture in this case would indicate a moderate degree of pernicious anæmia.

A test meal (½ pint of thin gruel) subsequently analysed in the Physiological Laboratories of University College revealed a complete achlorhydria.

Treatment for avitaminosis by special diet and drugs (Redoxin, vitamin C) and Radiostoleum (vitamins A, B and D) was now instituted but the animal rapidly became completely immobilized. It was therefore killed by chloroform, and the brain and chord were fixed in situ prior to their removal. No abnormalities were seen on naked eye inspection of the vertebral column, the cord membranes, or in any of the internal organs.

Sections of the spinal cord examined microscopically showed no gliosis or other indication of any repair process having taken place during the period of functional recovery. Loss of myelin and destruction of the white matter of the posterior and lateral columns extended continuously from the mid-cervical to the mid-lumbar region (figs. 1 A, B and C). This was the only case in which a small area of demyelination was found in the brain, viz. the left cerebral hemisphere.

A Green Monkey (*Cercopithecus sabæus*) was killed on account of epileptiform fits recurring daily for six days. The clinical features of one fit, personally observed, were as follows:

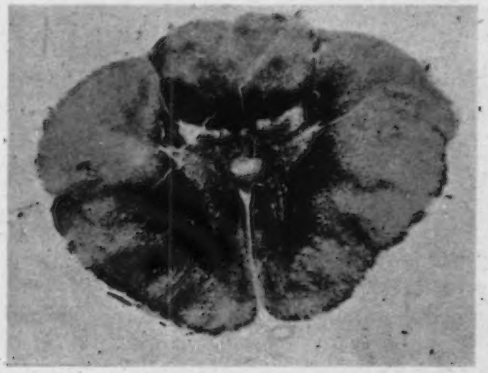

FIG. 1 A.

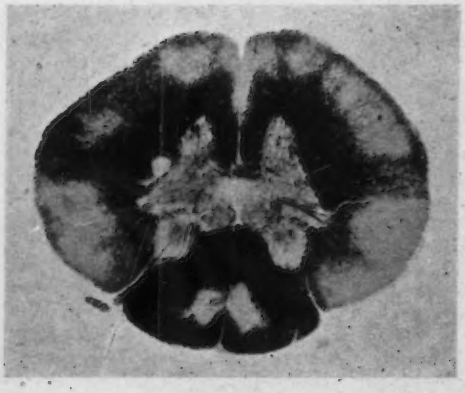

FIG. 1 B.

FIG. 1.—Spinal cord of Toque Monkey, showing demyelinated areas of primary degeneration. Weigert-Pal × 12. A, 14th thoracic segment. B, 1st lumbar segment. C, 4th lumbar segment.

After a few momentary spasmodic movements of the head and facial muscles, the animal rolled over on its side, apparently unconscious, with dilated pupils and all limbs extended and rigid. There was no cry nor any evacuation of bladder or rectum, and the tongue was not bitten. The fit lasted a few minutes only and was followed by coma (? sleep).

During its stay in hospital, the monkey was unable to use its hind legs, which remained flexed in a condition of spastic paraplegia. There was also some weakness of the fore limbs, but no tremor of the hands. Detailed clinical examination was impossible as the animal was furious when aroused and bit savagely.

At autopsy diverticulosis and focal abscess of the colon was found, but no other visceral lesion. The blood showed leucocytosis. The brain and spinal cord were fixed in situ by the gravitation method. No gross lesions thereof could be detected. Frozen sections of the cord stained by Scharlach R, showed fatty areas of demyelination in the posterior and lateral columns of its dorsal segments. Sections taken from the medulla and the cervical, dorsal and lumbar segments of the cord stained by Weigert-Pal and other special methods, showed the typical demyelinating lesions of subacute combined degeneration confined to the posterior and lateral columns of the mid-dorsal cord segments only. Sections of the cerebral peduncles, pons, cerebellum and of the rolandic, parietal and occipital areas of the cerebral cortex were examined histologically, but showed no appreciable lesions. It was not practicable in this case to histologize serially the whole brain, hence it is possible that foci of cerebral demyelinization may have been missed. The association of such foci with clinical "fits" in monkeys has been recorded by Scherer and others.

A Stair's Monkey (*Cercopithecus albogularis stairsi*) eight and a half years in the Menagerie, was admitted to hospital in March, 1936, on account of so called "cage paralysis," as indicated by weakness of the hind legs. Intention tremor of both hands was then a prominent symptom; the monkey could use both hind legs in climbing but walked with a stiff unsteady gait. Loss of power in the hind limbs gradually increased and twenty-one days after the onset of the disease there was complete flaccid paralysis of the hind legs and tail. By hauling itself up the bars of its cage with its hands, the monkey could reach the perch, astride of which it

would sit for hours with its paralysed legs hanging helplessly down—a characteristic attitude adopted by such patients (fig. 2).

FIG. 2.—A Stair's Monkey showing characteristic attitude of flaccid paralysis of hind legs due to subacute combined degeneration of the spinal cord.

The monkey was killed and immediately after death the central nervous system was fixed in situ. On removal of the brain and spinal cord no lesion was apparent on naked eye inspection of the skull, spine and cord membranes, nor in any of the internal organs. Sections of parts of the brain and of the whole spinal cord were stained by modifications of Weigert-Pal and Marchi methods. It was found that the degeneration changes were continuous in the white matter of the cord in all segments from the 2nd cervical to the 2nd lumbar inclusive. In the cervical region the lesion is limited to the left lateral columns. The disintegration of the myelin sheaths of the nerve fibres begins at the periphery and extends inwards affecting the ventral, lateral and dorsal columns of the cord. In the cervical region the lesion is limited to the left lateral columns. The extent of the lesion in the white matter is greatest in the 8th thoracic segment where it involves the ventral and lateral columns from the periphery inwards for more than half their thickness (fig. 3). In this case the dorsal columns are affected in the 12th thoracic and the 1st lumbar segments only. The grey matter appears to be normal in all segments of the cord. The demyelinated regions consist of a loose neuroglial network; in the mesh of which large fat-laden corpuscles are seen near the unaltered white matter (fig. 4). The axis cylinders in the degenerated regions are much diminished in number. No abnormality of the blood could be detected in this case.

I will now describe a case of primary combined degeneration of the cord in another Stair's Monkey which, after treatment for seventeen weeks, regained full

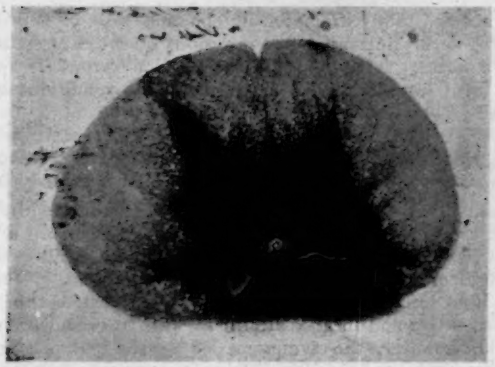

FIG. 3.—8th thoracic segment of spinal cord. The lesion involves the lateral and ventral columns for more than half their depth. Marchi stain.

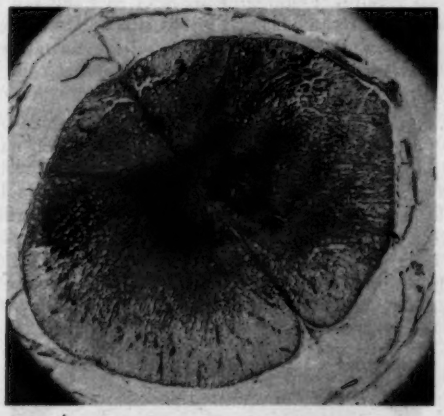

FIG. 4.—Demyelinated region from lower dorsal segment. × 14. Hæmatoxylin and eosin.

use of its palsied limbs and apparently made a complete functional recovery, followed after two years and seven months, by a recurrence and intensification of symptoms.

The animal first showed signs of the disease in July, 1937, when it was admitted to the Zoo hospital with intention tremor of the hands, a wobbling gait, a loss of power and ataxia of the hind limbs. It could not jump, and had difficulty in climbing up to its perch, on which it would sit for hours in the characteristic attitude already illustrated.

The condition of the monkey's blood before treatment was:

Hæmoglobin 95 per cent., colour-index 1·1, R.B.C. 4,200,000, leucocytes 19,800, of which there were 66 per cent. lymphocytes, 31 per cent. polymorphonuclears, 2 per cent. large mononuclears and 1 per cent. eosinophiles. Mast cells and nucleated red

corpuscles were absent. Polychromasia and poikilocytosis of R.B.C. was evident. *Treatment* was by weekly intramuscular injections of 2 c.c. of "Campolon" continued for twelve weeks. A few nucleated red blood corpuscles appeared in the blood after the third injection, after which the blood condition showed progressive improvement.

On November 10, 1937, the hæmoglobin was 105 per cent., colour-index 0·9, R.B.C. 5,800,000, leucocytes 20,000 of which 71 per cent. were polymorphonuclears, 26 per cent. lymphocytes, 2 per cent. mast cells and 1 per cent. eosinophiles.

After the ninth injection of "Campolon," the paresis of the hind legs was perceptibly less and the monkey was able to jump up to its perch, on which it could now maintain its balance without support. On November 30, all clinical symptoms, except slight volitional tremor of the hands, had disappeared. Normal power had returned to the hind limbs, and the monkey was returned to the Monkey House where it remained active and in good health for two years and seven months. On August 10, 1940, however, the symptoms of spastic paraplegia returned; the animal was able to walk, though with stiff ataxic movements of the hind legs and bilateral foot drop. On August 19, complete flaccid paralysis and loss of sensation in both hind limbs supervened. The monkey could now move only by pulling itself forward with its fore-limbs, dragging its hind legs and tail helplessly. Treatment by "Campolon" was resumed, but without effect. On September 6, the rectal and vesical sphincters became paralysed with resulting incontinence. The animal was therefore killed as incurable and the brain and spinal cord were immediately fixed in situ.

Post-mortem Examination.—Externally there was considerable wasting of the hind-limb muscles. Internally: No abnormality was found on naked eye inspection of the thoracic and abdominal organs, the endocrine glands, the lymphatic, osseous, generative, circulatory systems. Central Nervous System: No lesion of the brain or spinal cord could be recognized by naked eye inspection. Morbid Histology: Destruction of the axis cylinders and myelin sheaths of the nerve fibres in the spinal white matter was most pronounced in the lateral columns. The demyelinized areas were seen as a delicate open mesh-work of glia fibres, in parts of which compound granular corpuscles have replaced the degenerated nerve fibres (fig. 5). There was

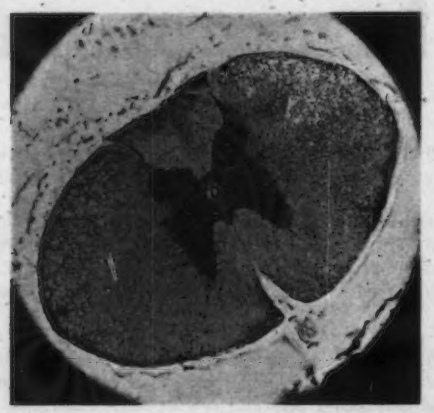

FIG. 5.—Section of mid-dorsal region of cord of monkey after treatment.

no inflammatory reaction nor any attempt at repair of any part of the destroyed area which extends from the upper cervical region to the lower part of the lumbar enlargement. In the spinal grey matter, some of the large anterior horn cells were atrophied.

Another case of subacute combined degeneration of the spinal cord that was treated by "Campolon" occurred in a Patas Monkey (*Erythrocebus patas*), an adult animal in good condition that had been one and a half years in the Zoo, without previous illness.

History.—On August 1, 1939, the monkey was reported to be suffering from weakness and loss of power in its hind legs. On examination, spasm and incoordination of the hind legs were noted. The monkey could shuffle about its cage but was unable to jump or to use its legs in climbing. There was volitional tremor of both hands and loss of sensation in the hind limbs and tail.

The vesical and rectal reflexes appeared to act normally, the other reflexes were not obtained as the animal was savage.

Blood Examination.—August 5: Hæmoglobin 77 per cent., R.B.C. 6,400,000, i.e. within normal limits, and of normal appearance. W.B.C. 10,683. Paresis of hind limbs now much worse. Treatment by weekly intramuscular injections of 2 c.c. of "Campolon" was commenced and continued for six weeks. After the third dose some return of muscular power was observed and after the fifth dose the animal could support its weight on its hind limbs and could perform its customary dancing movements on its toes. By October the monkey, having quite recovered was returned to the Monkey House where it remained active and in good condition for eleven weeks, when it was found dead. At necropsy the cause of death was found to be peritonitis following an ulcer of the colon, believed to be traumatic, and secondary pyæmic abscesses in the liver.

The histo-pathological features of the spinal cord were as follows:

Sections stained by Scharlach R and by the Marchi and Weigert-Pal methods show fatty degeneration and demyelinization of the anterior, of the posterior and of parts of the lateral conducting tracts in the cervical and dorsal regions of the spinal cord. Staining by hæmatoxylin and eosin and by Masson's stain showed in addition to demyelinization an infiltration of inflammatory cells (histiocytes) and atrophy of some of the motor cells of the anterior horns. There was no appreciable proliferation of neuroglial elements.

Histological examination of numerous sections of the spinal cords from the two treated cases reveals nothing to indicate that during their periods of functional recovery there was any regeneration or repair of the destroyed tracts in the cord. The temporary restoration of function—over a period of two and a half years in one case—is difficult to explain.

The histological picture of primary degeneration of the spinal cord in monkeys appears to be indistinguishable in its main features, from that seen in the cord lesions of subacute combined degeneration in man. In both species there is the same kind of progressive degeneration of the white matter of the lateral, the posterior, or the ventral columns, with a maximal destruction in the dorsal spinal segments. The primary lesion is not a sclerosis, but a true softening with fatty degeneration of the myelin sheaths and subsequent removal of the debris by compound granular corpuscles and the disappearance of the axis cylinders without any inflammatory

reaction or gliosis. In the spinal grey matter there is usually a secondary atrophy of some of the large multipolar cells of the anterior horn.

In the earliest case examined (that of a Green Monkey killed seven days after the first appearance of symptoms) degeneration of the lateral columns was already far advanced in the dorsal spinal segments. In this case, the initial stages of the lesion appeared to have arisen near the periphery of the lateral and posterior columns of the upper cervical region; in which vacuolation and phagocytic histiocytes (compound granular corpuscles) are seen (fig. 6), and recognized in Scharlach R stained preparations as cells stuffed with globules of ruby-coloured fat. The function

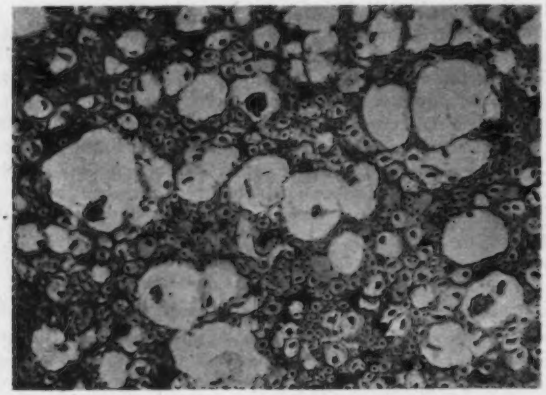

FIG. 6.—Early stage of lesion in lateral columns of mid-dorsal segment of cord of a Green Monkey killed seven days after disease was first noticed. See vacuoles, in some of which are compound granular corpuscles, in others fragments of axis cylinders. × 250.

of these cells is somewhat obscure: they appear in any lesion of the central nervous system that causes myelin to form fat, are said to phagocyte fat and myelin and to act as scavengers in clearing away the debris of broken-down nerve fibres; but such an hypothesis could be substantiated only by the study of living tissues. Eventually these corpuscles disappear from the lesion leaving only the delicate open network of glia fibres which is pathognomonic of the disease.

The similarity in the histological features of primary combined degeneration of the cord in monkeys and the human disease known as subacute combined degeneration is however no criterion for the belief that they are identical diseases, either in their ætiology or in the patho-

logical processes required to produce isomorphic lesions in two zoologically allied, yet obviously different species. Much more comparative study is required before the identity of the two diseases can be established. It is suggested that the ætiology of subacute combined degeneration might be enlightened by further experimental investigation; bearing in mind however that a similar, if not identical, disease is naturally acquired in captive monkeys.

It is regretted that no detailed histological study of the distal ramifications of peripheral nerves has been possible in the monkeys noted.

Treatment.—The preventive treatment of certain animal diseases associated with dietary deficiencies was instituted at the Zoo in 1927 by Dr. Vevers and was followed by remarkable improvement in the health of the monkey house population, with consequent reduction of death-rate and the elimination of rickets amongst Apes and Old-World Monkeys.

If we assume that the disease under consideration is a manifestation of avitaminosis a review of the patient's diet is desirable.

Pre-War Diet for Monkeys

Fruit	*Vegetables*	*Animal Protein*
Apples	Carrots	Tinned milk
Bananas	Potatoes (raw and boiled)	3j of condensed milk
Dates	Cabbage (raw)	to 4 oz. of water
Ground nuts	Wheat and maize in grain	
	Whole meal bread with bone meal	

Supplementary

Halibut Oil (vitamins A, B and D) 2 drops daily on sugar.
Grapes and oranges occasionally.

The only imperfection in this diet is a probable insufficiency of animal protein.

Monkeys in their wild state are mainly, but not exclusively, herbivorous. All the year round they forage through the forest trees devouring the eggs and young of birds, lizards and other small creatures.

Drug Treatment by "Campolon" (Bayer product)—a liver extract said to contain vitamins A, B_2 and B_6, in addition to hæmopoietic factors—was followed by temporary functional recovery of two monkeys:—A Stair's Monkey in which functional recovery, though lasting two and a half years, was followed by relapse, and a Patas Monkey that unfortunately died from intercurrent disease eleven weeks after recovery. For comparison with the treated cases, there is the case of the Toque Monkey that received no treatment but made a spontaneous but complete recovery followed by relapse after one year. It is necessary therefore to suspend

judgment on the effect of treatment pending further experimental investigation.

My grateful acknowledgments are due to Mr. T. J. F. Barrington, F.R.C.S., for advice and assistance in the histological work and practical help in the field of investigation. Dr. J. G. Greenfield for confirmation of histological findings and advice. Dr. Carmichael for clinical examination of cases. Sir Philip Manson Bahr for advice on treatment. Mr. H. Corbett, technical assistant, for histological and hæmatological work. Mr. Warwick James, F.R.C.S., Mr. A. T. Jones and Mr. Martin Duncan, F.R.M.S., for illustrations. To the Zoological Society for permission to reproduce fig. 2.

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APHASIA IN CHILDREN.

By ERIC GUTTMANN,

Working with a Grant from the Rockefeller Foundation

(From the Nuffield Department of Surgery, Oxford.)

"APHASIA in children" is almost always used as synonymous with congenital aphasia. For instance, Ewing's pioneer work and his book deal almost exclusively with children who have never learnt to speak. Acquired aphasia in children is much less known, and in the literature on the subject many contradictory statements are encountered. Some doubt has even been expressed as to whether such a condition exists. This view must be traced back to the first French writer on the subject, Cotard (1868), whom Bernhardt cites as saying:

> "Il est extrèmement remarquable que, quel que soit le côté de la lésion cérébrale, les individus hémiplégiques depuis leur enfance ne présentent jamais d'aphasie . . . et cela même quand tout l'hémisphère gauche est atrophié."

Though this view was soon challenged by Bernhardt (1897) it received a tacit acceptance owing to the fact, it may be assumed, that few neurologists were able to collect large experience in this particular field. Bernhardt had stated: "True aphasia is not rare in childhood; it is a frequent symptom of infantile cerebral hemiplegia, mostly transient, rarely permanent. It is mostly motor in type."

Freud (1897), in his classical monograph on Infantile Cerebral Paralysis, saw and defined the problem clearly. He distinguished (1) true aphasia—being a disturbance of the speech faculty already acquired; and (2) retarded development of speech in children who had not yet acquired speech when they were taken ill, or were in the process of learning to speak. In the latter case the disturbance was not to be regarded as a focal symptom, since it might also occur as a sign of poor general cerebral development.

Of recent writers, Nadoleczny (1926) in discussing aphasia distinguishes its different causes. Following head injury, he says, aphasia is rare as a sign of local injury to the speech centre. Most cases recover within a few weeks, i.e. more rapidly than adults. "In cerebral hemiplegia

generally the speech is lost for some time, often for months, entirely, or with the exception of a few words such as 'yes,' 'no,' 'papa,' which can be repeated. Understanding of speech is preserved, as a rule. In spite of the paralysis, speech recovers within from a few weeks to a year."

L'Hermitte (1934) writes: "Les Aphasies acquises: Leur étiologie est la même que chez l'adulte; ce qui est particulier à l'enfant c'est que, de règle, un syndrome aphasique si intense et si extensif qu'on le suppose, est rapidement dissipé."

Ford (1937) says: "In children whose speech functions are fully developed cerebral lesions cause aphasias of the same types which are seen in adults. . . . Cerebral lesions in children who have not yet begun to talk or in whom speech function is not fully developed usually result in complete loss of speech, not fractional loss of speech as in older children. In time, the child will usually begin to talk just as an infant first learning to speak. First inarticulate sounds are made, then single words, later phrases, and finally short sentences. A childish lisp often persists for years. It seems impossible to reconcile the speech disturbances resulting from cerebral lesion in infants with any type of aphasia seen in adults."

Not many cases of infantile aphasia are on record, and only very few are described in adequate detail. André Thomas (1935), who says: "Sans être exceptionelles, les observations d'aphasie de jeune age ne sont pas très frequentes," reports one case, a boy of 6 with motor aphasia which quickly improved. Taillen (1937), who thinks "L'aphasie motrice est rare chez l'enfant," publishes three cases occurring during the course of pneumonia in children of 3, 3½ and 8 years respectively, all of which recovered very rapidly.

Poetzel (1926), Brunner and Stengel (1932), and Wagner and Mayer (1933) have reported single cases of sensory aphasia occurring in children of 7, 4 and 12 years respectively.

Three problems stand out in these publications on acquired aphasia in children: its incidence, the clinical picture, and the prognosis. I shall discuss these three questions in the light of my material, which, coming from a neurosurgical department, is limited to cases of injury, tumour and abscess. Thus, cases of the so-called infantile hemiplegia are not included. This simplifies the problem by excluding the question of the relationship between mental defect and aphasia in early acquired severe or widespread brain damage.

The transient loss of speech in children in the course of toxic-infectious illness will not be discussed here; in none of my cases could the speech

disturbance be accounted for by general impairment of cerebral function, clouding of consciousness or stupor; such disturbances often complicate the picture of aphasia in toxic-infectious conditions.

Incidence.

Thirty cases of primary hemisphere affection in children of 14 years and under were collected, all but five verified by operation and/or autopsy. Of these five, three were depressed fractures of the skull with well defined neurological symptomatology, the fourth a cerebral thrombosis following status epilepticus, the fifth a space-occupying lesion. Among the verified cases there were 6 injuries, 6 neoplasms, 12 abscesses, 1 thrombosis.

The age distribution was as follows:

Up to 2,	4,	6,	8,	10,	12,	14 years of age.
1,	2,	5,	6,	4,	8,	4. Total 30.

The incidence of aphasia, in regard to localization, is indicated in the following table:

	Aphasic	Non-aphasic
Left frontal	4	2
Left temporal	5	-
Left parietal	2	-
Combined	3	-
Total	14	2
Right frontal	-	5
Right temporal	-	6
Right parietal	1	1
Combined	-	-
Bilateral	1	-
Total	2	12
	Total 30	

These figures show clearly that aphasia in left hemisphere lesions in childhood is not at all rare, and examination of the few apparent exceptions proves that it is just as regular a symptom in children as in adults. The first of the two negative cases (S. H., Case 1,252), a boy of 13 years, had an abscess in the region of the left frontal pole, not encroaching on the speech region; the other one (T. A., Case R.I. 12,187), a boy of 7 years, also had an abscess following a punctured wound of the forehead which occupied the left frontal pole without reaching the speech centre or the motor area. The patient with the right parietal lesion who developed aphasia was a case of severe injury to the right parietal region, and it is very likely that a contre-coup injury to the left hemisphere was responsible for the speech disturbance.

It may be interesting to compare these findings with those of Bailey (1939), who "is impressed by the rarity of aphasia" (p. 346). He has six cases of left hemisphere tumours in children (Cases 75, 77, 78, 79, 82, 83). Of these the first was a parieto-occipital case in which blindness would have prevented the diagnosis of alexia. In Case 78, a parietal tumour, the symptomatology was entirely spinal. Case 79 was a tumour on the base of the middle fossa which in adults would not necessarily lead to aphasic symptoms; moreover, it was a child of 1 year 7 months in whom the recognition of disturbed understanding would have been difficult. Of the three remaining frontal cases the first is described as obstinate and disobedient; the second did not speak; the third had difficulty in expressing himself and in naming objects.

Clinical Picture.

Considering the figures in the table, it is surprising that the rarity of aphasia in children is so often emphasized, and I think this can be accounted for only by lack of understanding of the clinical picture of aphasia in children. Aphasia in the adult is mostly diagnosed or sought for when the patient complains of difficulty in his speech—which children do not do—or if he uses wrong names for objects; in other words, apart from cases of complete motor aphasia, the early diagnosis of aphasia is commonly based on subjective or objective word-amnesia. The clinical appearance in children is different, and the signs of aphasia in a sick, apathetic, shy and often morose child are easily overlooked unless specially sought. Most of these case records were not made with special reference to infantile aphasia, nevertheless in fourteen out of sixteen aphasic cases, we find "absence of spontaneous speech," "unwillingness to speak," "poverty of speech," "telegram style," hesitancy and dysarthria quoted as symptoms which must be regarded as indicative of aphasia in the light of the clinical picture so frequently seen during recovery from complete motor aphasia in adults. One temporo-parietal case (aged 11) showed disturbed auditory and visual word-comprehension as the leading symptom; another one (aged 14) showed a similar symptomatology after a severe head injury with multiple fractures of the skull and a right-sided paresis. Symptoms like those in the first-mentioned fourteen cases are liable to be disregarded unless they are accompanied by more impressive aphasic manifestations. In nine of our fourteen cases these motor symptoms were the leading manifestations of speech disturbance, but only in five were there no other signs of involvement of the speech function. In view of the subsequent discussion it may be mentioned here that the ages of these

five cases were 2, 4, 6, 7 and 8 years respectively; the localization, frontal 3, parietal 2.

Poetzl first drew attention to the fact that in cases of temporal lobe aphasia in children the initial logorrhœa observed in adults may be absent. Our findings suggest more than that; all cases of aphasia in children under 10, wherever the anatomical lesion, tend to show reduction of spontaneous speech, varying in degree from complete mutism to what is described in case records as "reluctance to speak" or "unwillingness to speak." All cases in the lower age classes (2, 4, 6 years) correspond to this rule, whereas two cases without reduction of speech output are over 10 years old. Among the cases of 10 years or over there are, however, three (aged 10, 11½, 12 years) which show hypo-spontaneity of speech.

The relationship of the symptomatology to the anatomical lesion can be discussed in only a few well-localized cases. The localization was well defined in one of the "talkative" high age-group (temporal abscess), and fairly well defined in the other one (cricket ball injury over left mastoid with right lower facial weakness, no sensory loss, and contraction of the right homonymous visual fields, especially in lower quadrants). In the "reticent" high age-group one was well defined (temporal abscess), the other two being a cerebral thrombosis with right hemiplegia and no sensory loss and no visual field defect in the one case, and a very large left hemisphere glioma in the other. This distribution makes it appear likely that the age is a decisive factor in producing the hypo-productive aphasic picture in children; under the age of 10 every lesion in the speech field tends to reduce the output of spontaneous speech; above the age of 10, some patients still respond in the infantile way whereas others produce the picture generally seen in the adult.

The apparent uniformity of the picture in children does not prevent further differentiation. On the contrary, one can clearly distinguish those cases in which the understanding of spoken language is affected from those where only speech production is impaired. In the majority of my cases the lesions are not well enough localized to allow definite correlations to be established between the site of the lesions and the clinical picture. Moreover, owing to the varying need for operation, degree of general illness, duration of stay in hospital, and other external circumstances the notes on the aphasic symptoms differ very much in completeness from one case to another. I shall therefore quote three examples: one frontal lesion, one temporal and one temporo-parietal, which show the clinical variety.

(1) *Frontal Aphasia.*

J. K. (R.I. 16,322), aged 6 years, admitted 28.6.41 after having bumped his head into a lamp-post when riding his bicycle. Never unconscious; compound fracture of left fronto-parietal region. Operation: removal of bone splinters; toilet of lacerated brain; suture of dura.

30.6.41: Well awake and easily approachable. Right facio-brachial monoplegia. No spontaneous speech. Does not answer questions nor repeat words; makes attempt at speaking, moves tongue and lips; does not get a sound out. Understands and carries out simple requests; points to parts of his body or to objects in the room, when asked to. Follows neurological examination easily except the requests to blow or to whistle.

2.7.41: Paresis improves. Begins using his right hand. Sits up. Speech unchanged, but nods "yes" and "no" in reply to questions. Hums a tune.

3.7.41: Carries out movement of whistling or blowing. Speech: produces some noises like nasal vowels (eng or ung).

4.7.41: No spontaneous speech, no answers, no naming of objects; but repeats words, the vowels adequately, the consonants slurred and indistinct. Counts from one to ten, when urged; pronunciation so bad that one would not recognize the individual numbers taken out of sequence.

5.7.41: Counts on request. Repeats "good-bye." Says "pardon" once automatically. No sounds when jokingly threatened; does not say "daddy" or his sister's name.

7.7.41: Does not speak spontaneously, though otherwise he is very lively indeed. He counts on request, names all objects at hand correctly, though his speech is still very slurred and indistinct. He answers questions in one-word sentences only; but is able to carry on some sort of conversation in that fashion.

8.7.41: Says "good morning" spontaneously. Expresses some wishes in words.

9.7.41: First little conversation recorded. Says his father is out buying food for Johnny in London. He will have a sweet shop when he is grown-up. Pronunciation difficult, slurred.

14.7.41: Out of bed and very lively, but well-behaved and easy to manage. No weakness of face and arm. He speaks spontaneously, though perhaps less than one would expect considering his general activity. He counts, recites nursery rhymes, names objects. His speech is slow; he forms sentences, short, as one would expect, with no grammatical errors. His pronunciation is still very slurred, though he improves a little, with effort. Follow-up, October, 1941. There is nothing abnormal in his speech now.

(2) *Temporal Aphasia.*

J. W. (R.I. 4,209), aged 11·6 years; admitted Radcliffe Infirmary 8.9.39. He was perfectly healthy up to the middle of July, when he developed middle ear catarrh This subsided after treatment with M & B. On August 2 some anomaly in his speech was noticed; on the 3rd he became drowsy and had several convulsions. He was operated on, and a subdural collection of pus removed. He made a good recovery, and only a slight hesitancy with words was noticeable. On August 14 the temperature flared up, the wound was reopened, and he improved again. On August 21 he was found unconscious. He was operated on again, the opening in the dura enlarged, the brain needled, but no abscess was found. From this time to his admission he was drowsy, and his speech very bad. He also gradually lost power in his right arm. On admission: Large fungus above left ear. Bilateral papillœdema (2D). Complete right-sided hemianopia. Right flaccid hemiplegia with extensor plantar response. Marked postural loss in right arm and leg. His

spontaneous outgoing speech was almost absent; he had a marked nominal aphasia, and was slow in carrying out spoken and written commands. He was paraphasic and paragrammatic, and had great difficulty in simple arithmetical problems.

After his general condition had improved under conservative treatment, his spontaneous speech was still like this: "Two weeks on end July . . . end of July I was ill, and when I . . . July . . . end of school . . . and September . . . end . . . go to school again . . . August, September . . . August I was free."

He was operated on on November 2, when the fungus was removed, and he made a very slow recovery, interrupted by several attacks of meningeal infection. He was discharged on February 2, 1940, after having been afebrile for a fortnight. He was still hemiparetic and hemianopic, and there was considerable postural loss in his right arm, less in his leg. During the period of recovery his speech function fluctuated: For twenty-four hours after the operation he did not speak at all. Then he started speaking single words, later small sentences, telegraphic in style. His auditory comprehension was satisfactory for simple commands, but for anything a little more complicated not perfect. In March, 1940, his speech was still telegraphic in style but he could express more easily what he wanted to say. In May, 1940, his speech was described as no longer entirely telegraphic; he used simple sentence form, even if he was apt to omit the articles.

In May, 1941, I found him speaking quite freely. He was not telegraphic in style, but made a number of syntactical and paraphasic errors. His verbal understanding was not disturbed, as far as the usual aphasia tests go, but his auditory understanding of little problems was below the standard of his age. His arithmetic was also below his age standard, and his intelligence, tested by non-verbal tests (Koh's block design and Raven's Matrices) corresponded to a mental age of 12 (Chron. Age 13). His hemiplegia, hemianopia and sensory disturbance still persisted.

When examined on February 2, 1942, his speech functions had not changed very much. His spontaneous speech was still slow. He articulated with effort, mispronounced some consonants, made pauses at wrong places, and made syntactical mistakes. In the Binet Vocabulary tests he was definitely above average; but his aphasic handicap was very noticeable in the way he defined things, e.g. eyelash "Piece of things . . . like hair, but sticking out under the eyebrow." His result in the Raven Matrices test corresponded now to an I.Q. above 100.

(3) *Temporo-parietal Aphasia.*

J. J. (No. 820), aged 10·6 years. On July 2, 1932, at 2 p.m. patient was struck by cricket ball just above left mastoid. He was not unconscious and remembered being struck. At 5.30 he fell ill, vomited and it was noticed that he was confused and did not seem to understand. When seen by Professor Cairns late in the evening, he showed constriction of the visual fields to the right; no paresis or sensory loss. He had some nominal aphasia, considerable difficulty in understanding, marked dyslexia and some difficulty in writing. In a more detailed examination the next morning, his spontaneous speech was found to be slow. He enunciated clearly, but had difficulty in forming sentences. He had great difficulty in naming common objects, and he understood spoken language imperfectly. On July 7 his comprehension both for oral and written commands had improved, but he still had considerable difficulty in naming objects. His reading aloud was still paraphasic. On the 12th he understood the usual spoken and written commands, and he was able to read a newspaper paragraph with a few mistakes. He wrote to dictation and copied correctly. On July 19 he answered the question: What is the meaning of the word envy? "Oh, I am not quite sure how I . . . if somebody's got something nicer than the other . . . there's something in the Bible about it . . . If somebody

. . . I envy you . . . they envy . . . I don't quite know how to pronounce . . . I can't quite . . . don't know what to say . . . I can't . . . I know what it means but can't say what it means properly. I, er . . ." Reading aloud was paraphasic. There was very little difficulty in finding names of objects, but some of his words were paraphasic. On September 22, apart from some slight perseveration and paraphasia no abnormality in his spontaneous speech was detected. His auditory understanding was undisturbed, his reading comprehension slow. He named all the objects shown to him correctly. On December 2 his spontaneous speech was perfectly normal, and he carried out all spoken and written commands without hesitation. He read aloud fluently.

Follow-up, 1942. Letter from his mother: "All his school life he has been perfectly normal, not brilliant at work, but just average. He has always been an out-door boy. He has been so normal, that we had really all forgotten the old head injury. He passed his school certificate at his first entry with 5 credits". He joined the Navy in November, 1940, went to sea, then worked for a commission. During this time he had two probably epileptic fits, but in spite of this, he passed the final examination, passing the 17th out of 70.

Prognosis.

For the discussion of the prognosis, ten cases are available—four recent and six old ones. Considering how much the cases differ pathologically and in the degree to which they have been examined and tested, the number is obviously too small for a statistical comparison, and they can be reviewed only individually.

Recent Cases.

These include three cases of head injury and one of cerebral thrombosis.

T. P. (R.I. 14,886), aged 4. 18.4.41: Knocked down by a motor-cycle. Bruising on left forehead. No fracture. Red cells in cerebrospinal fluid. Very drowsy. Generalized convulsions one and a half hours after accident. Cried when roused, but did not speak. A fortnight after admission still extraordinarily silent; when pressed responded with a few unintelligible syllables. Carried out requests, named objects, but pronounced words as if his tongue were too big for his mouth. Speech gradually less slurred.

15.5.41: Discharged. Pronunciation distinct. Speaks with nurses and other children.

Follow-up January, 1942: There is not the slightest indication of any speech disturbance. His school report is satisfactory.

A. C. (R.I. 14,324), aged 6 years. 19.3.41: Kicked by horse. Unconscious. Simple depressed fracture right temporo-frontal region. No neurological signs. For some days after recovery of consciousness, when he was perfectly co-operative, he made no attempt to speak.

8.4.41: Discharged. Only residual symptom a slow and rather halting type of speech. More excited than previously, and hasty tempered.

11.5.41: Speech recovered.

Follow-up, January, 1942. There is not the slightest indication of any disturbance of speech. His school report is satisfactory.

J. K. (R.I. 15,322), aged 6 years. His case record is given above as an example of the clinical picture of motor aphasia and its recovery.

These three patients illustrate the good prognosis of purely motor aphasia in young children; they all had traumatic lesions, and it is possible that the prognosis of aphasia after abscess or lobectomy is different. However, the third case (J. K.) had a considerable amount of lacerated brain tissue removed from, or very near, the Broca area. The picture was that of a complete motor aphasia, with very little general disturbance of cerebral function—the boy was never unconscious. The mode of recovery corresponded to that seen in adults after localized lesions of the frontal speech area, but the speed of recovery was remarkable. After three weeks the boy had practically recovered.

The fourth case of this group differs from the other three, showing, in addition to complete expressive aphasia, gross disturbances on the receptive side. These point to a more extensive lesion. Also the lesion in this case, probably thrombosis with softening, differs so much from that in our traumatic cases that it does not lend itself easily to comparison. However caused, the case indicates that motor and sensory aphasia combined have a more serious prognosis than motor aphasia alone.

B. S. (R.I. 15,758), aged 12 years, was a normal intelligent boy. On 6.6.41 an abscess in an old spina bifida was evacuated by lumbar laminectomy under a general anæsthetic. After operation he had a series of epileptic fits, and, when waking up, he was hemiplegic on the right side and aphasic. He had no sensory loss and no field defect.

18.6.41: Lies silent in bed, wide awake; turns his head right and left and makes large groping movements with his arms, particularly his right arm. When talked to or asked to do something he cries readily, but a few seconds later he smiles again.

(Put your tongue out!) Opens his mouth wide without showing his tongue, in spite of several repetitions of the request.

(I put my tongue out). He imitates it.

(Your name?) No reply; pouts, grimaces, but makes no sound.

(Count!) He produces some faint sounds in some sort of rhythm like one, two, three, but he does not go on with counting, nor does he repeat numbers shouted at him.

Given a little book he holds it in front of his face, his arms outstretched, vertically off the bed. He tries to turn pages with his left hand, but does not give the impression that he can read. He accepts and sucks a sweet with gusto. He watches my writing and tries to grasp my pen. Given a little doll, he holds it firmly in his left hand. After a while he drops it and takes up the book again.

(A tobacco pipe): Tries to hold it with his right hand and to take it to his mouth, but drops it on the way.

(Screwdriver): Grins at it, handles it quite nicely with his left hand with the correct grip. He gropes for his book again and holds it with his left hand, together with the screwdriver.

(Scissors): Takes them in the same hand which holds the other objects and drops all together.

(Another sweet): He tries to grasp it with his left hand. It is not possible to make him say "please."

20.6.41: Changes continuously from smiling to moaning and crying. He opens his mouth on request and offers his left hand. He nods "yes" and "no" in reply to questions; but it is difficult to say how much or how little he understands. Mostly he shakes his head in refusing to do or to say things. He says "yes" indistinctly, and he also hums a tune (unknown to me)—"ta-ta ta ta." He recognizes a sweet, grins and opens his mouth. He does not grasp it unless told to. He munches it with pleasure. Given several objects he responds in two ways; either he rejects them or he takes them into his left hand and puts them into his mouth.

26.6.41: Given a percussion hammer and a tuning fork he puts them into his mouth. A watch he takes up towards his mouth, but half-way stops. Later he demonstrates with his left hand the use of a toothbrush, a ball, and a pencil, but not that of a screwdriver. He scribbles with the pencil, and on request he writes something like a 5 and a 3, mirror-fashion.

He does not point to nose or eye at verbal request, but holds a watch to his ear when told. He still cries very readily.

30.6.41: Given the Binet Picture Vocabulary set and asked to point to individual pictures.

(Key): looks from one picture to the other, hesitates at the watch then points to the key.

(Cow): behaves similarly; no success.

(Shown the cow and asked: "Is this a cow?"): he nods "yes."

(Cat): no success; does not decide for any of the objects.

(Procedure as before): Does not recognize or accept it.

(Umbrella): no success, either way.

(Bicycle): points to it with little apparent difficulty.

(Union Jack): correct.

(Drum): no success.

Objects asked for in writing: no success; the writing does not seem to convey any meaning to him.

Objects shown to him and given him to handle.

(Dart): recognizes it, takes it correctly into his left hand and indicates its use.

(Gimlet): demonstrates its use.

(Safety-pin): recognizes it, succeeds in opening it with his left hand and makes a good attempt at closing it.

Picking out coloured bits of cardboard.

(Yellow): correct after a long time, after many repetitions of request, but without other help.

(Red): correct.

(Blue): picks white.

(Green): correct.

(Black): no success.

Matching colours; correct.

Counting cardboard pieces.

(Give me 5): gives 6.
(Give me 2): correct.
(Give me 3): correct.
(Give me 5): gives 6.
(Give me 4): correct.
(Give me 5): correct.

2.7.41: To command he closes his eyes together or separately, looks sideways. Opens his mouth, shows his tongue, puts his tongue into his cheek, licks his upper lips, moves his tongue sideways. He does not whistle, blow or cough. He cannot imitate those actions which he cannot carry out on request.

4.7.41: Movements of eyes and tongue as before. Cannot whistle. His speech is limited to "yes" and something that may be "please." He expresses "yes" or "no" by head-shaking. His facial expression is adequate, and no longer exaggerated. His auditory understanding is still limited to very simple commands.

9.7.41: Called "nurse" last night. Repeats to-day a few words (two, bloke, punch, box). His pronunciation is slurred. On verbal request he points to his ear, mouth, my tie, the carnation on his table, but he does not understand "nose" or "hair."

10.7.41: Spontaneous speech absent; cannot name any object.
Repeating words: Similar to yesterday.

Finding objects on picture cards.

(Key): moves with his finger over the part of the card where it is but cannot decide between cat, key, watch.
(Cat): correct.
(Umbrella): correct.
(Car): points to dog.
(Key): no success.
(Moon): correct.
(Bicycle): correct.
(Cock): no success.
(Drum): correct.
(Girl): correct.
(Cat): correct.

Unable to express anything in writing or to write to dictation. Copies slowly.

11.7.41: He is now up and walks with a right spastic hemiplegia.

20.10.41: He can say a few words; his pronunciation is laboured, slow, badly articulated. When given a picture to describe he does it entirely in disconnected words, nouns and infinitives. He finds the names of all the Binet pictures, except one; but he has great difficulty in pronouncing the names. He has no difficulty in finding objects on a picture card on verbal request. He understands spoken questions and requests, complicated ones slowly. He reads very slowly, 20 monosyllables in a minute. He reads a number of comparatively difficult words up to age grade 8 (such as scramble or beware), but sometimes has trouble with very simple ones (such as her or wet). He has no difficulty with isolated letters, and his reading comprehension is very good. He cannot write to dictation, but copies from writing and print. He reads and writes figures and knows the four operations. He can name no colours, but finds most of them correctly on verbal request. He has no difficulty in drawing or constructing. In a non-verbal intelligence test he scored a mental age of 13·6 years.

LONG-DISTANCE PROGNOSIS.

Case No.	Pathology	Duration of stay in hospital	Aphasia on discharge	Total period of observation	Residual symptom at end of observation
1 J. W. (R.I.4209)	Otogenic abscess	4 months, 10 days	Considerable	2½ years	Hesitant paraphasic & slightly para-grammatic
2 J. P. (204)	Otogenic abscess	1 month	Recovered	5 years	None
3 G. L. (206)	Post-traumatic abscess	1 month, 20 days	Slight	5 years	Speech slow some difficulty in reading
4 J.P. (R.I.2636)	Head injury	2 months, 20 days	Practically recovered	3 years	Slight: slurs words when excited
5 J.J. (820)	Head injury	1 month	Slight	10 years	None
6 D. S. (2228)	Head injury	1 month	Slight	5 years	None

In considering the long-distance prognosis one has obviously to keep in mind the severity of the original lesion which is difficult to express in comparable figures. The length of stay in hospital as given in the table serves as a rough indicator, as all cases were discharged as soon as their cerebral condition made it possible. Only the last case on my list, a private patient, was taken home comparatively soon.

The first case was an exceptionally severe one, as regards the lesion and surgical condition. Summarizing the others, one might say that, if after four weeks aphasic signs are still noticeable, the prognosis as to final outcome has to be more guarded, or in other words that aphasia in children recovers within four weeks in benign cases. The last case, however, demonstrates that slight residues at that time may still fully recover. Case 1 is still under observation and nothing definite can be said about the ultimate result, though the course to date—a slow, but continuous improvement—leads one to think that he will finally recover for all practical purposes

ASPHASIA AND INTELLIGENCE.

Students of aphasia are much interested in the relationship of speech disturbance to intelligence. Some hold the view that aphasia is due to a disturbance of conceptual thinking, others think that intellectual dis-

turbances observed are consequent on the "aphasic handicap." However that may be, it is of interest to learn how far aphasia in children causes a retardation in their intellectual development. These six cases do not contribute greatly to answering this question, as three of them have not been examined particularly from that point of view. However, gross intellectual backwardness would certainly have been observed and complained of by their relatives on the occasion of the follow-up visits or inquiry. Case 5 was under very careful observation at Eton, and the reports received made it certain that his intellectual efficiency was up to its previous standard, and he passed his school certificate with five credits. He joined the Navy and passed his final examination for a commission. Case 6 was regarded at school as less brilliant in mathematics than he was before his accident, but he got a first when passing out of Dartmouth, winning the mathematics prize. He got prizes in all subjects in the examinations during his training as a naval officer.

Case 1 was re-examined two years after his first admission. Having been away from school for two years (on account of his hemiplegia rather than his aphasia), he was behind his age in scholastic tests; in reading, spelling and arithmetic his performances corresponded to the standard for 11-year olds (he was 13 years at the time of the examination). But in all these tests his aphasic difficulties, slight as they were, could not be excluded as a contributory cause. In non-verbal intelligence tests he was one year behind his age. In a more recent examination (February, 1942) his speech function had not changed much, but in both verbal and non-verbal intelligence tests he was well up to his age standard. One of the more recent cases (B. S., page 213) still grossly aphasic, scored above his chronological age in a non-verbal intelligence test four months after the onset of his cerebral illness.

The final test of the importance of the aphasic disturbance in intellectual retardation, if any, would be provided by comparing the final outcome in left-sided lesions with similar disturbances affecting the right hemispheres. I have been able to follow up these three cases:

P. N. (R.I. 4,892), a girl aged 12 years, was admitted 28.11.38. Following chronic trouble with her right ear and a recent septic skin condition she developed signs and symptoms of cerebral abscess. Located by ventriculography in the right temporal lobe, it was removed whole, and the child was discharged recovered on 16.12.38. On inquiry by letter, her mother wrote of her (1941): "she is a fine girl, but cannot take no hard work. She gets a bit cross with herself."

I. P. (R.I. 3,668), aged 12 years, was admitted on 11.9.38. She suffered from osteomyelitis of the right frontal bone following a local infection, and developed

a right frontal abscess which was excised with good surgical result. Discharged on 25.2.38. Follow-up October, 1941: She had finished school, leaving last July from top standard. She is now anxious to find work, but has not yet been successful owing to external conditions.

D. S. (R.I. 283), a boy aged 6 years, was admitted 18.1.39, and discharged 24.3.39, after a right frontal abscess had been completely removed. Follow-up October, 1941: Is still in Infant School, which he should have left by now. His educational ratio is 79. He is described as "such an intelligent boy, suffering from such a handicap."

These cases, though not so thoroughly examined as one would wish, at least illustrate that intellectual or emotional disturbances are likely to be the result of general brain damage by the disease process or by the excision of parts of the brain, and not a result of an aphasic disturbance which indeed may not be present.

Summary.

Thirty cases of cerebral hemisphere lesions in children have been examined with a view to comparing with adult cases the frequency, clinical picture, and prognosis of acquired aphasia in children.

In this group aphasia occurred with the same regularity as in adults.

In all cases under ten years and in some between ten and fourteen the clinical picture is uniformly that of diminished speech production, with dysarthria and telegraphic style in the recovery period; this is equally true of cases with frontal and temporal lesions. The latter show disturbances of speech-receptive as well as expressive.

The recovery from aphasia of the purely motor type is surprisingly rapid, and most cases with a reversible lesion have recovered within four weeks.

Some cases of aphasia which were submitted to intelligence tests showed very little, if any, impairment; some cases with lesions of the right hemisphere and no aphasia did show retardation of intellectual development. This, if confirmed by a wider survey, would point to the brain damage rather than to the aphasia as the factor responsible for the disturbance of intelligence.

My thanks are due to Professor Hugh Cairns for his suggestions and criticisms and for his permission to use his clinical material. I am also indebted to Mr. J. B. Pennybacker, whose interest in the condition led to this study. I am grateful to Dr. C. P. Symonds for giving me access to his notes on Case J. J. (No. 820).

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CEREBELLO-OLIVARY DEGENERATION: AN EXAMPLE OF HEREDO-FAMILIAL INCIDENCE.

BY F. PARKES WEBER AND J. G. GREENFIELD.

AMONGST examples of familial developmental abiotrophy of the nervous system are many family groups in which probably no histological examination has ever been made; for instance, some of those in which tremor commencing after adult age, slowly increases, and ultimately tends to take on an "intention" character, and in which the affected members live long and in some respects clinically resemble cases described as hereditary ataxia. In regard to collected literature and discussions on cerebellar degeneration and hereditary ataxia we must refer to Hassin and Harris (1936), and to the monograph on Hereditary Ataxia by Julia Bell and E. A. Carmichael (1939).

The record given here is of the case of a woman with hereditary cerebello-olivary degeneration, in whom the disease commenced with

Genealogical Table showing the Heredity of the disease

♂ = ♀ (died at 77)

♂ = ♀ (Mrs. M. B., died at 78)

—Twin girls, one died at 3 weeks, the other at 7 years

—♀ M. L. B., aged 45

—♀ Mrs. E. M. F., aged 49 (two sons, one died in infancy; the other, aged 12 years, is living and normal)

—♂ still-born

—♂ died in infancy

—♂ died in infancy

—♂ died in infancy

—♂ born Nov. 2, 1890, died in infancy

unsteadiness of gait at 60 years of age. She died at 78, and the result of the post-mortem examination is described. Her mother died at 77 and evidently suffered from the same disease, which first showed itself at 60 in the same way, by unsteadiness of gait. The only children of the patient who lived beyond childhood, two daughters, aged 45 and 49 respectively, have been clinically examined, and are found to be suffering from a mild degree of the same disease, which in both of them commenced at the age of 40 with unsteadiness of gait.

Case Report (Dr. Parkes Weber).

Mrs. M. B., aged 78, was admitted to hospital on August 14, 1941, with the following history: About the age of 60 she began to suffer from unsteadiness of gait and weakness in legs with some slurring of speech. These symptoms gradually increased, but she continued to be able to get about a little with the aid of a stick, though of late she had not been able to extend her legs completely. There was obviously a condition of progressive dementia and for the last twelve months she had hardly been able to keep awake. Her sight and hearing had been failing and of late there had been incontinence of urine and fæces. She was still able to some extent to answer questions. The patient was also suffering from recurrent attacks of a kind of senile prurigenous purpuric eruption, almost limited to the left forearm and hand, though there was itching and scratching of other parts also.

In the hospital.—By ordinary and X-ray examination the heart was enlarged to the left and there were calcified plaques in the aortic arch. Calcified plaques were also visible in the abdominal aorta and in the region of the cœliac axis. No enlargement of the liver, spleen or superficial lymphatic glands. Considerable scoliosis. Marked decalcification of vertebræ. Calcification of costal cartilages. Thickening of the cranial vault. Pituitary fossa, apparently normal. Brachial blood-pressure: 220/80 mm.Hg. Blood-count: Hæmoglobin 62 per cent.; erythrocytes 3,250,000; colour index = 1·0; leucocytes 5,500 (polymorphonuclears 71 per cent.; lymphocytes 25 per cent.; monocytes 1 per cent.; eosinophils 3 per cent.). Thrombocyte-count: 320,000 to 400,000 per c.mm. of blood. Blood sedimentation accelerated: first hour 42; two hours 83. Blood-Wassermann and Kahn reactions: negative. Urine: specific gravity 1017; acid; trace of albumin; no sugar; some leucocytes but no tube-casts were found in the centrifuged sediment. Eyes and pupils (Dr. C. Markus): Nothing abnormal excepting slight incipient cataract both sides. No spontaneous nystagmus (at rest). Patellar and ankle reflexes: active on both sides. Superficial abdominal reflexes: not obtained. Plantar reflexes: flexor on right side; doubtful on left side. Sensation: no evidence anywhere of anæsthesia or hyperæsthesia, excepting tenderness in connection with passive movements of the flexed lower extremities.

The patient seemed always to be apathetic and drowsy, lying in bed with her legs drawn up. The upper limbs were relatively little affected. There was general emaciation but no obvious localized muscular atrophy anywhere. She scratched herself very much. The intermittent prurigenous purpuric (ecchymotic) eruption in the left upper limb continued and it is doubtful whether treatment by vitamin C did any good. The general condition further deteriorated. Bed-sores developed. During the last few days she seemed to be hardly conscious and did not even scratch herself any more. She died on November 3, 1941.

Family history.—The patient's mother had suffered from similar symptoms, which began at 60 years of age with unsteadiness of gait. She gradually lost the use of her legs and arms and control of her sphincters. Mental degeneration was complete before her death at 77. The patient (Mrs. M. B.) had 9 children, 5 boys and 4 girls. One of the boys was stillborn and the others died in infancy. Of the four daughters two were twins, one of whom died at 3 weeks and the other at 7 years. The remaining two daughters are living, aged 45 and 49 respectively, and both of them at 40 commenced to show slight unsteadiness of gait, as their mother did at 60. There is no history of in-breeding in the family. The patient (Mrs. M. B.) and her husband were not blood-relatives, nor were her mother and father. Both the daughters have been examined.

The younger of the two sisters, Miss M. L. B., aged 45, who is still able to do her work as a domestic servant, says that she has always had some slight difficulty in walking, but that her real trouble commenced at 40 with unsteadiness of gait. At present she has a slightly staggering and "stiff" gait on a somewhat too broad base, slight deficiency of facial mobility (Parkinsonian-like), slight slurring of speech and slight intention-tremor in the left hand. No definite muscular ataxia by ordinary tests. No Rombergism. No nystagmus or anything abnormal in the eyes. Nothing abnormal in regard to nervous reflexes and sensation. Nothing abnormal in regard to examination of the thorax, abdomen and urine, excepting that a radiogram shows that the bronchial markings are somewhat increased at the right base. Brachial blood-pressure: 125/90 mm.Hg. Menstruation still regular. Blood-Wassermann reaction: negative. She likes her employment and feels better when she is working, but her employers are careful not to overwork her.

The elder of the two sisters, Mrs. E. M. F., aged 49, married at 30, and has had two children (both boys—one died soon after birth—the other is now 12 years old and has always been apparently bodily and mentally normal). Menopause at 46. She walks fast and easily, but somewhat unsteadily and on too broad a basis. This unsteadiness of gait was first noted at 40—the same age as that at which her sister's abnormality of gait was first noted. She is apparently able to live an ordinary normal life. In regard to speech there is some definite slurring, at least in certain words. No definite muscular ataxia by ordinary tests. Nervous reflexes normal. Nothing abnormal in regard to the eyes, excepting hypermetropia. No deafness. No tremor. No nystagmus. No definite stiffness of face. Sensation apparently normal. Nothing abnormal in regard to thoracic and abdominal viscera and urine. Brachial blood-pressure: 145/80 mm.Hg. Blood-Wassermann and Kahn reactions: negative.

Clinical Diagnosis.

It seemed obvious that the heredo-familial nervous disease was a developmental abiotrophy of some kind, but one was inclined to the diagnosis of a presenile encephalopathy, possibly of the Creutzfeldt-Jakob type. The extreme degree of general arteriosclerosis, however, made me doubtful. Dr. Greenfield's post-mortem histological examination has finally decided in favour of parenchymatous cerebellar atrophy, together with extreme generalized arteriosclerotic changes. Thanks are due to Dr. H. K. Lauber and Dr. K. Blum in regard to the clinical examination of the case.

Post-mortem examination.—Emaciated body, with legs bent up and decubitus. Extreme calcareous atherosclerosis of the thoracic and abdominal aorta and branches; some of the mesenteric arteries superficially resembled thick, firm, india-rubber tubing. The heart (weight, 250 grm.) showed relative hypertrophy of the left ventricle and some atheroma of the aortic valve. The right and left kidneys (75 and 100 grm. respectively) showed nephrosclerosis with adherent capsules and little cysts. The liver (875 grm.) and spleen (100 grm.) showed nothing special macroscopically, nor was anything abnormal noted in the other abdominal organs (not all were examined) and lungs. The calvarium was sclerosed. Brain (880 grm.): cerebral convolutions appeared shrivelled, with excess of cerebrospinal fluid in the leptomeninges. Pituitary gland: macroscopically not abnormal. Much calcification of the arteries at the base of the brain.

The brain and whole spinal cord, together with pieces of some of the other organs were sent to Dr. Greenfield for histological examination.

Histological Report and Discussion.

By J. G. Greenfield.

Microscopical examination of the viscera and muscles.—All the viscera were the seat of severe arteriosclerotic changes. These were most obvious in the kidneys where the walls of many of the medium-sized arteries were so greatly thickened in a concentric manner that the lumen was almost completely obstructed. Many of the glomeruli were completely sclerosed, and there were localized superficial areas of fibrosis, with some small celled infiltration and degeneration of the tubular epithelium. Elsewhere there was a tendency to dilatation of the convoluted tubules. The glomerular arterioles showed only a moderate degree of hyaline degeneration.

In the spleen also there was great concentric thickening of the vessel walls, and some hyaline degeneration in the small vessels in the Malpighian bodies.

The liver showed little abnormality except moderate fatty degeneration.

The muscles examined showed a very severe degree of simple atrophy affecting a large proportion of the fibres. In these fibres the sarcolemmal nuclei appeared more numerous than normal, and the fibres were only 5 to 10μ in width, but they retained their cross striation. There was widespread increase of fibrous tissue. These changes are in keeping with disuse atrophy but may have been contributed to by poor vascular supply.

Examination of the brain and spinal cord.—The brain and cerebellum were small, but no disproportionate shrinkage of the cerebellum was obvious. The sulci of the brain were wide as in many senile brains. On section of the brain small brownish areas with cavitation in their central parts were seen in the anterior part of the corpus striatum on the left side and in the upper and anterior part of the thalamus on the right side. The vessels in the putamen were abnormally prominent and were surrounded by a narrow zone of brownish discoloration. Apart from these areas in the basal ganglia no softenings or discolorations were visible macroscopically in the central nervous system.

Microscopically the larger areas, visible to the naked eye, showed rarefaction of the tissues with the formation of small lacunæ. There was throughout these areas loss of nerve cells and fairly dense neuroglial sclerosis and they were full of pigment which stained with Prussian blue. Some smaller foci of neuroglial scarring with deposition of blood pigment were also seen. The narrow zone round the vessels showed only absence of nuclei and rarefaction of the tissues. No other definite abnormality was seen in the basal ganglia. In the cortex the nerve cells contained

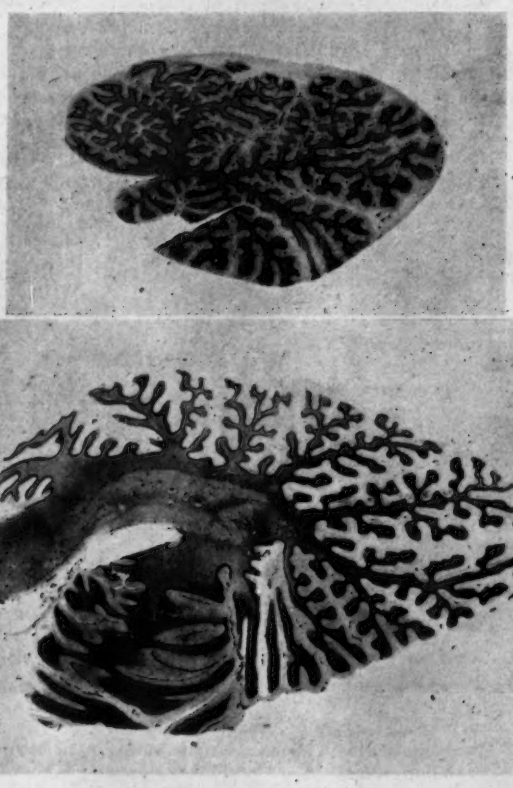
some excess of lipochrome pigment, but there were no "areas of paling" and no senile plaques were found. The vessels throughout the brain were rather thick walled, and those in relation to the larger scars in the basal ganglia had their lumen partially obstructed by atheroma. These changes were all clearly of vascular origin. In the mid-brain and pons also small foci of ischæmic degeneration were found; in the anterior part of the red nucleus on one side there was a dilated and thrombosed vessel, round which there was some loss of nerve cells and deposition of blood pigment. In the opposite nucleus ruber there were narrow zones round the vessels in which the myelin stained poorly. Numerous areas of ischæmic degeneration were seen in the ventral part of the pons. These were most apparent in sections stained by Loyez myelin method counterstained with carmine. They appeared as areas of pallor or loss of myelin staining following the course of a vessel through the ventral half of the pons, chiefly in its deeper parts. At about the mid-level of the pons a small area of loss of tissue was present in the centre of the ventral half on one side and another in the outer part of the mesial fillet on the opposite side (fig. 1). The latter had caused Wallerian degeneration of this part of the

FIG. 1.—Transverse section of pons, showing ischæmic area in ventral part on one side and another involving the mesial fillet on the opposite side. Loyez myelin stain.

fillet at higher levels. When examined by Loyez stain it was clear that these areas were of vascular origin and were not due to systemic degeneration of neurons. In many areas in the pontine nuclei the nerve cells at one side of a group had disappeared, their place being taken by small round nuclei; the remainder of the neurons in this group were usually normal. Pallor of myelin staining was not obvious along the line of transverse fibres arising in groups of neurons which had disappeared, but affected both transversely and vertically coursing fibres along the

line of a vessel. Both in the affected groups of nerve cells and in the areas of myelin degeneration there was fairly dense neuroglial scarring with the presence of many large astrocytes with thick processes. The great majority of the neurons of the nuclei pontis were perfectly normal and the transverse fibres and middle peduncle stained darkly. There was however some shrinkage of the ventral half of the pons. Except for the lesion in the region of the fillet the tegmentum pontis was normal.

Cerebellum.—On section of the cerebellum in the sagittal plane there was an obvious disproportion between the size and width of the folia on the upper surface, which were shrunken, and those of the tonsils, flocculus and the anterior part of the inferior vermis which appeared to be fairly normal. This was still more obvious



(*a*)

(*b*)

FIG. 2.—Sagittal sections through (*a*) the vermis and (*b*) the lateral lobe of the cerebellum, showing atrophy of folia on the superior surface. Iron hæmatoxylin, van Gieson.

in large sections in this plane, in which the granular layer of the tonsils was much wider than that in other parts of the cortex (fig. 2). The shrinkage was everywhere

greatest in the anterior part of the superior cortex and was rather greater here in the vermis than in the lateral lobes. As one passed backwards and round to the inferior cortex there was a gradual increase in the width of the layer. But except for the tonsils and flocculus no part appeared to be of normal thickness. Under low microscopical powers the molecular layer also was seen to be shrunken proportionately to the granular layer and to be somewhat rarefied. Much greater, however, than the shrinkage of these layers of the cortex was the disappearance of Purkinje cells. Only an occasional shrunken cell could be seen in the most affected parts of the cortex, such as the anterior-superior parts of the vermis (lobulus centralis), and elsewhere they were so sparse that it was easy to find folia containing none. Most of the Purkinje cells seen were shrunken and stained poorly, again with the exception of those in the tonsils and flocculus, most of which stained normally. Even in these lobules the Purkinje cells appeared to be rather reduced in number and many were shrunken, but neither change was of greater degree than is found in many senile arteriosclerotic brains. Except in the most affected folia the basket fibres were fairly well preserved, and in sections stained by the Gros-Bielschowsky method these fibres stood out prominently (fig. 3). Torpedo-like

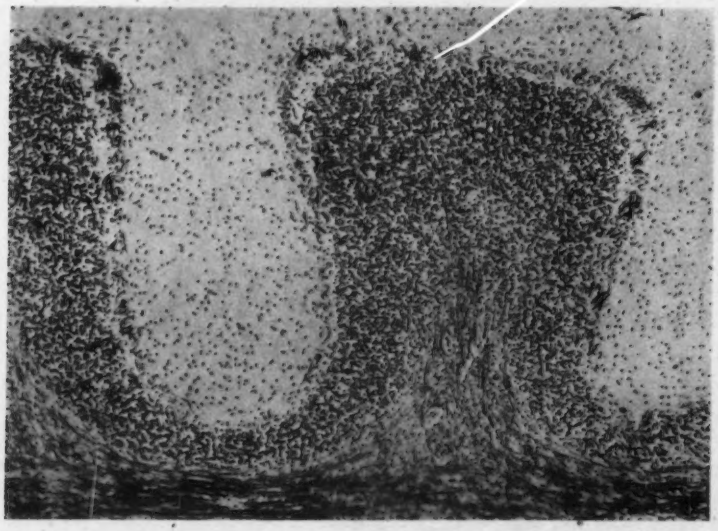


FIG. 3.—Cerebellar folia, showing loss of Purkinje cells with preservation of basket fibres. The granule cells in this region are rather more sparse than normal. Gros-Bielschowsky—alum carmine.

swellings on the axons of the Purkinje cells were fairly numerous in folia which were moderately affected. None were seen in folia from which almost all the Purkinje cells had disappeared and nowhere could more than one be found in a high power field. The myelinated fibres which lie in the layer of Purkinje cells were as well stained in the most affected folia as in the least affected. In the more affected folia

the granular layer was thinner and its cells sparser than normal, and a layer of Bergmann cells lay in the Purkinje cell layer, slightly separated from the granular layer. Gliosis in both molecular layer and white centre was proportional to the degree of degeneration and was everywhere isomorphic. The white centres showed a varying loss of fibres, never very severe. No fat was found in sections stained by Scharlach R. The dentate nucleus and roof nuclei appeared perfectly normal and the superior cerebellar peduncle stained well.

FIG. 4.—Low-power view of inferior olives at upper end of medulla, showing great loss of nerve cells especially in dorso-medial part. (Lower, right hand area indicated by arrow.) Nissl—toluidin blue.

Medulla.—Unfortunately the medulla had been cut off short in removing the brain and only the upper end was available for section. Here at the junction of the pyramid and inferior olive on one side there was a thrombosed vessel surrounded by considerable deposition of blood pigment, and slight pallor in the staining of the myelin sheaths. There was at this level obvious shrinkage of the ventral part of the medulla and narrowing of its antero-posterior diameter. The inferior olives looked smaller than normal, but projected to some extent on the surface.

Microscopically there was a striking difference between the condition of the nerve cells in the dorsal and ventral halves of the olive, though they were nowhere quite normal either in size or number. Those in the dorsal part were without exception shrunken, and in some areas none was to be seen (fig. 4). In a few places there was also an absence of axons, and in some of these areas the endothelium of the capillaries was studded with small granules which stained with Prussian blue. In several areas in the dorsal half there were groups of small club-shaped end-swellings on the axons (fig. 5). Some of these groups lay in areas from which

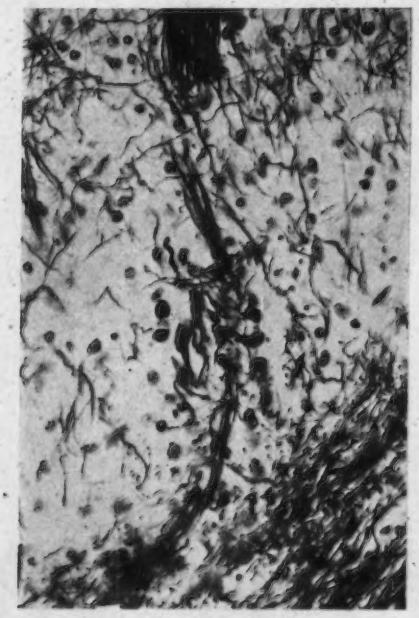


FIG. 5.—Area of inferior olive showing a group of end-swellings on axons going to the neurons of the inferior olive. Gros-Bielschowsky—alum carmine.

nerve cells had completely disappeared. They occurred in more isolated fashion both in the grey matter and in the hilum of the olives. There was, however, very little pallor of myelin staining either in the hilum or in the capsule of the olives. The neuroglial felt-work was fairly dense throughout the olives and their hilum, but no difference could be made out in this respect between the dorsal and ventral halves.

The inferior peduncles of the cerebellum appeared fairly normal as did also the whole of the dorsal part of the medulla. No abnormality, except collagenous thickening of the intra-medullary vessels and numerous corpora amylacea, was found in the spinal cord.

Discussion.

The classification of the disease in this family is a matter of some difficulty. From the clinical standpoint its members were clearly suffering from a progressive disease of the cerebellar system. And if the histological changes found in the case examined may be considered as typical of the disease in other affected members of the family, its chief incidence appeared to be on the Purkinje cells of the cerebellar cortex. The microscopical examination leaves little doubt that the changes in the pons, like those in the basal ganglia and mid-brain, were of vascular origin and were not part of the familial degenerative disease. So far then we have the picture of parenchymatous cerebellar degeneration. But in addition there was degeneration in the inferior olives which, although slight by comparison with the cerebellar degeneration, is not found in many cases of primary cortical degeneration. It has, however, been present, in greater or less intensity, in the only familial cases of cortical cerebellar degeneration which have so far been described, as well as in some other cases of the same nature. Such cases of combined degeneration of the cerebellar cortex and the inferior olivary nucleus have been classified by Kinnier Wilson, following the lead of Hänel and Bielschowsky, as olivo-cerebellar atrophy. Hassin and Harris have considered them as incomplete forms of olivo-ponto-cerebellar atrophy. On the other hand Gordon Holmes in describing his familial case considered that the olivary degeneration was secondary to that of the cerebellar cortex, an opinion in which he was followed by Schob. Apart from that described by Holmes (1907), the only family which appears to belong in this group is that of Akelaitis, although in it the disease ran a much more rapid course and was fatal in less than two years. In the family described by Hänel and Bielschowsky there was no definite evidence of cerebellar disease in the other members. They were described as neurotic, the grandmother's sister had torticollis and several had kyphoscoliosis. The chief symptom in the patient whose nervous system was examined was para-myoclonus, and there is a doubtful history of similar movements in a sister of the patient. It is therefore doubtful whether this can be considered as a familial case. The sclerosis of the olivary nuclei in this case was described as severe, but its incidence on the olives was not detailed. In Holmes' case and in those of Akelaitis,

in all of which the cortex on the superior surface of the cerebellum was especially degenerated, the greatest degeneration of the olives was found in their dorsal folds. This is in agreement with the work of Holmes and Grainger Stewart (1908), who examined the cells of the inferior olives for retrograde chromalotysis after acute and sub-acute partial lesions of the cerebellar cortex, and found that the dorsal half of the olives corresponded to the superior surface of the cerebellum. In Kufs' case also there was a similar special incidence of the degeneration on the dorsal half of the olives. He does not give details of the localization of the cerebellar degeneration. On the other hand, in Schob's case of primary cortical cerebellar degeneration the ventral and dorsolateral parts of the olives were most degenerated. He does not state what parts of the cerebellar cortex were specially affected except that the neo-cerebellum was more affected than the palæo-cerebellum and the lateral lobes more than the vermis. He considered, however, that the degeneration of the olives was secondary to that in the cerebellar cortex—a retrograde degeneration. Gordon Holmes pointed out that a long standing interruption of physiological function might lead to degeneration of neurons, even though their axons were not directly involved in the degeneration. It is on this basis that we can most easily interpret the olivary degeneration as secondary or retrograde, seeing that, according to modern teaching, the termination of the olivary axons is as mossy fibres round the dendrites of the granular cells, and in our case at least, the granule cells were relatively little affected. However the degree of degeneration may have been sufficient to lead to retrograde degeneration of such labile neurons as those of the inferior olive.

If the olivary degeneration be considered as secondary to the degeneration of the cerebellar cortex it would appear that the term "cerebello-olivary" would describe the degeneration better than "olivo-cerebellar," which suggests at least that the degeneration of the olives was of equal importance to that in the cerebellar cortex. There appears to be little in common between such cases of cerebello-fugal degeneration and the cerebello-petal disease olivo-ponto-cerebellar atrophy, in which the degeneration is usually much greater in the olives and pontine nuclei and their axons than in the cerebellar cortex. In fact the latter may be entirely spared.

We therefore classify our case as a familial instance of cerebello-olivary degeneration, along with those of Gordon Holmes and Akelaitis, and do not follow Hassin and Harris as including cases of this kind in the group

of olivo-ponto-cerebellar atrophy. Only the examination of more familial cases of this nature can establish the justice of this position, but in the present state of our knowledge it appears to be logical.

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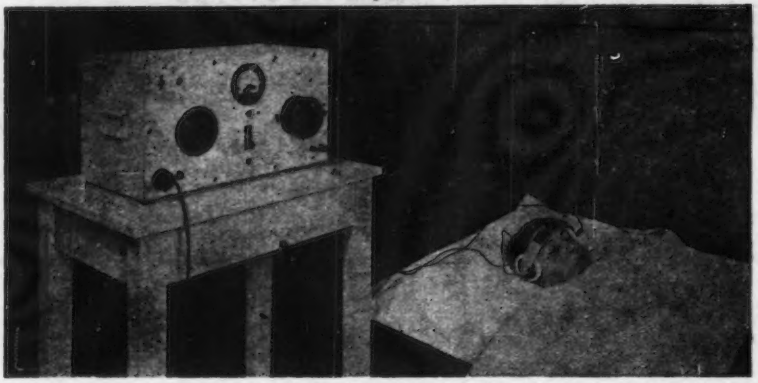

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Edited by F. C. BARTLETT, with the assistance of C. BURT, J. DREVER and S. S. ISAACS

Vol. XXXII. Part 4 **10s. 6d. net** **April 1942**

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